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BRAIN.

PART 1, VOL. 54.

QUANTITATIVE MANAGEMENT OF CONTRACTION IN LOWEST LEVEL CO-ORDINATION.

HUGHLINGS JACKSON LECTURE.[1]

BY C. S. SHERRINGTON.

COMPACT in Hughlings Jackson was a fine vein of pithy thought and phrase. Among its memorable examples stands that figure [1] of the nerve centres as rising in three tiers or levels. It gained common usage, and is witness to its author not least in the tacit and complete assurance that neural organization and co-ordination are inseparably one. Of it I think had he been with us to-day he would have judged no illustrations happier than the notable studies of asynergia, rigidity and tremor, and the modern advance in knowledge of their nature, which are our debt pre-eminently to clinicians of our own country. The nervous system is indeed both a form and a series of events. These have to be confronted together even for inquiry which concerns itself with function as its chiefest aim.

Hughlings Jackson describes "dissolution," his great analyst of the nervous system, as pulling to pieces from the top downwards to descend variously far. So likewise physiological experiment, but, for simplicity, starts lower. A rump of mechanism, a stump of spinal cord, these it interrogates through perhaps a single afferent for answer by a single efferent. Such virtuosity has of course its defects; one of them is the mutilation entailed. But its hope is, since bottom is basal, to reach bottom; though even there the elemental may not prove to be the simple.

MOTOR UNITS.

Of Jackson's three levels, simplicity's field of choice will lie in the lowest, the Jacksonian third. There, and at its simplest, is that old-fashioned if time-honoured entity, the motor centre. I hesitate to invite recontemplation of such oft-worn ground; yet in light of some fresh detail it seems to accrete endowment. With it, an initial problem, and nowhere more essential, is quantitative adjustment. Sampled by afferent stimulation the motor centre soon reveals that every reflex fractionates its muscle. The fractionation is not pushed so far as to run to the single muscle-fibre. Soleus (cat) has some 30,000 muscle-fibres and the long extensor of the digits some 40,000 [2]; but

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[1] Given January 29, 1931.

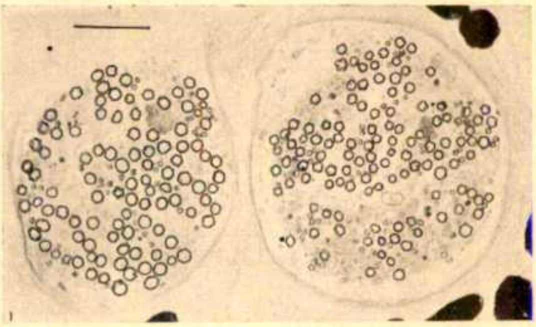


FIG. 1.—Showing the number and diversity in size of the motor nerve-fibres of a muscle. Nerve of *soleus* (cat); all afferent fibres removed, 179 fibres remaining, giving a tetanic contraction of 1,780 g. in the muscle. An accompanying branch of nerve of *gastrocnemius lateralis*, also deafferented. Fibre diameters of soleus average smaller than of gastrocnemius, *cf.* fig. 4. Photomicrograph × 128. (Eccles and Sherrington, 1930 [3].)

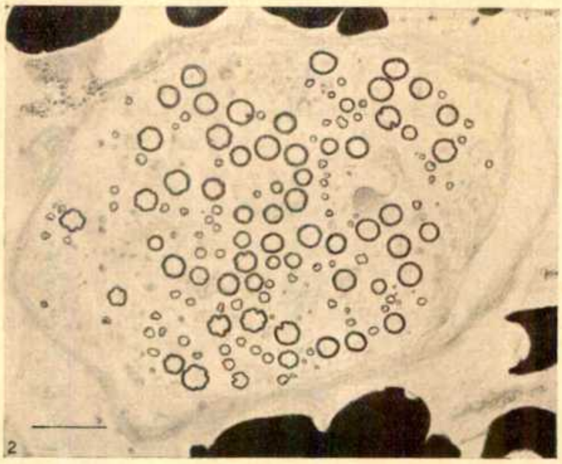


FIG. 2.—Portion of nerve of *biceps femoris* (cat); all afferent fibres removed; the motor fibres range in diameter from 2 μ to 18 μ. Photomicrograph × 320. (Eccles and Sherrington, 1930 [3].)

nervous co-ordination, as Hughlings Jackson said, is "based on the anterior horn-cell." That cell by its motor nerve-fibre innervates a whole packet of muscle-fibres, 150 and more. This packet of muscle-fibres together with its motor nerve-fibre constitutes what may be called for short a "motor unit." It is into these packets that the reflex fractionates its muscle. They give numbers not unmanageable—*soleus* (cat) consists of some 200, *extensor longus digitorum* 330, medial *gastrocnemius* 450 [3].

Such motor units yield a contraction-wave of some 2·5 g., and even of 9 g. contraction-tension [3]. A coarse unit, it would seem, to grade with. The more since its contraction runs on the "all or nothing" plan, so that to grade the strength of the stimulus, however carefully, does not arrive at grading the strength of the contraction-wave itself,

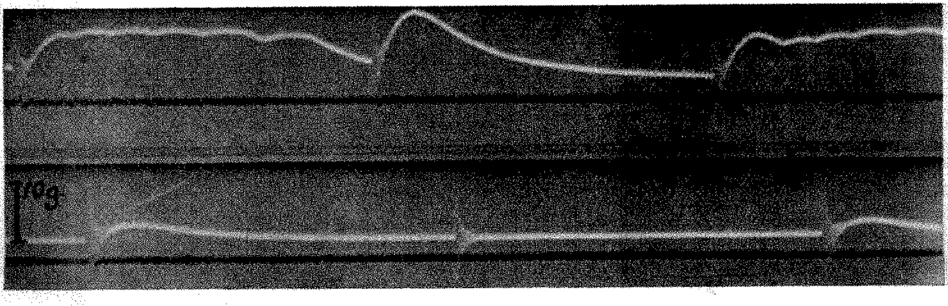


FIG. 3.—Contractions of single units of *soleus*, mechanically evoked by tapping the standard fixing the isolated muscle; the main motor spinal root to the muscle was cut; and one afferent spinal root (7th) only remained as the afferent supply of the muscle. The purely mechanical effect of the tap appears as a rapidly damped vibration. The "jerk" response is of one motor unit, as evidenced by myograph and galvanometer, in the lower line of the record; between the two reflexes is a tap which failed to elicit a response. The upper records are, to left, an initial response of two units of which one continues tetanically at 10 per sec. for 5 beats; and again to right; between them a larger response, ? of two motor units. (Eccles and Sherrington, 1930 [3].)

the contraction-wave being in so far a fixed quantity independent of the strength of its stimulus. In reflex action, however, we know that the single contraction-wave as an isolated event scarcely happens. These the contraction waves overlap to form tetanus. This tetanus when once the mechanical fusion of the component waves is *complete* yields in its turn a tension value fixed, in so far that no increase of strength or of rate of stimulus will change it further. This full tetanic tension value for the average unit is 10 g. in *soleus* (cat) and reaches 35 g. in gastrocnemius [3].

Such fixity of value for the tetanized motor unit allows reflexes which can ensure it to be tested for their share of a given muscle [4]. In this way it is found that in the limb practically no afferent nerve possesses the whole of any one muscle, and that every afferent nerve has some reflex share in practically every muscle.

The motor units which make up tibialis anticus (cat) number some 380; its spinal motor horn-cells are in effect the expanded receptive central ends of these motor units. Some of the motor units are larger than others, and to these attach doubtless the larger motor horn-cells. The overlap of central terminals on these large cells, if their density on the cell surface is as elsewhere, must be specially extensive, so that the large motor units will be the more widely at call and the more often in play.

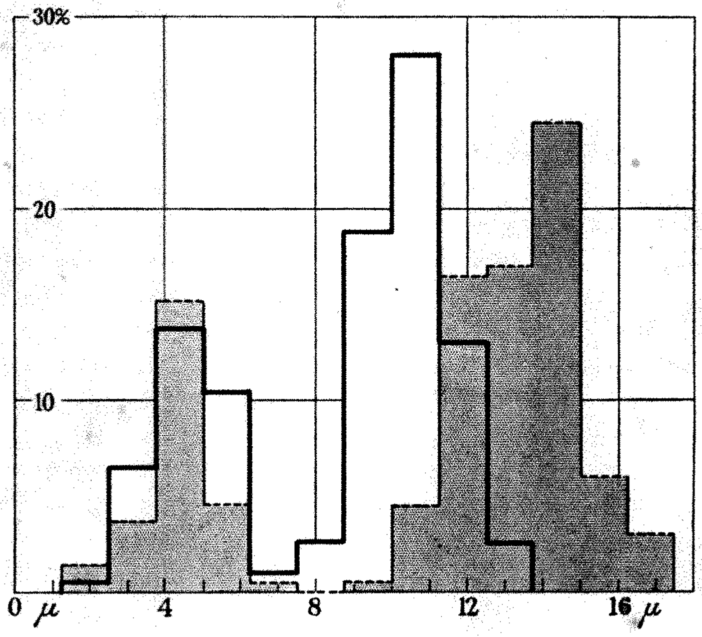


Fig. 4.—Motor nerve-fibre sizes in nerve of *soleus* and in nerve of *gastrocnemius* plotted against percentage numbers (ordinates) of the respective sizes. Deafferented preparation. Only myelinated fibres are enumerated. For *soleus* nerve the contour line is solid (——) and the contained area (except where overlapped by *gastrocnemius* chart) is blank. For gastrocnemius nerve the contour line is broken (— — —) and the contained area is stippled. Fibre sizes along abscissa line in μ. (Eccles and Sherrington, 1930 [3].)

Of the 380 motor units thus making *tibialis anticus*, the internal saphenous nerve under faradization can tetanize some 120, the popliteal 290, a dorsal digital 135; and so on. We may suppose the central terminals of these afferent nerves to play largely directly upon the motoneurones, since in the case of this relatively simple reflex, recent work discounts the invariable mediation of an internuncial neurone between afferent root and ventral horn-cell.

GRADES OF EXCITEMENT IN THE MOTOR CENTRE.

That many or most of these last are fully tetanized is shown by submitting them to additional excitation and their then yielding no additional contraction [5]. Motor units thus fully tetanized can be classed as *maximally* excited.

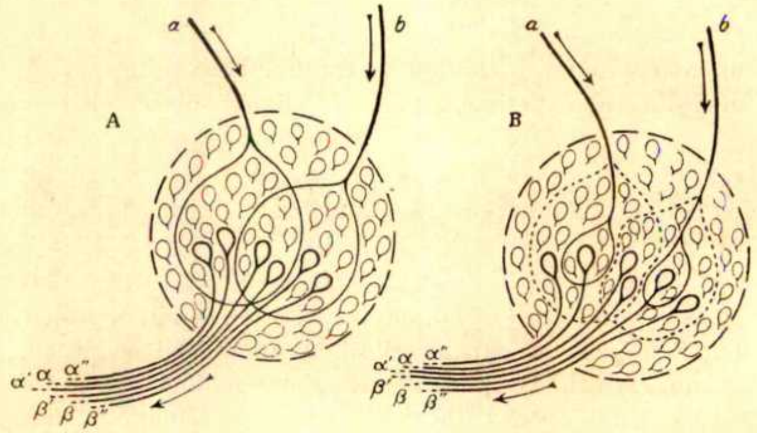
When we find in an experiment that full tetanic stimulation, say, of a plantar nerve, tetanizes 190 of the 380 motor units and stops at that, may we suppose that the anatomical limit of the number of motoneurones reachable by the afferent has been attained? Hardly, for the number thus found, within limits, can fluctuate quite rapidly during the course of an experiment [4]. A slight subconvulsive dose of strychnine, accelerating reflex recruitment, and shortening, as Bremer and Rylant showed, the reflex latency [56], will strengthen the response perhaps 25 per cent. Conversely, with spinal shock it shrinks.

The temporary upper limit represents therefore not the anatomical total which the nerve can reach, but some, often a large, proportion of that total, a proportion circumscribed by functional condition. And there is abundant evidence that besides those motoneurones which the afferent nerve thus excites, there are others, a subliminal fringe, on which it acts but fails to bring to discharge. The proof of this is that an excitation similarly subliminal from another source when brought to bear concurrently on this subliminal fringe does bring it to discharge [5, 6, 7]. Explanation of the variation in the number of motor units a given afferent nerve at different times will excite, may lie partly in subliminal excitation from some other reflex or central source being in or out of action on some of the motoneurones at the time.

At the opposite extreme from the subliminal fringe there obtains what we may term "supra-maximal" excitement. By combining tetanizing excitations say *via* two separate afferent nerves, the excitement of some motoneurones can be brought to "supra-maximal" in the sense of more than sufficient for full tetanic contraction of the muscle-fibres of their units. This is detectable by "occlusion" of contraction [5, 52], and it commonly happens under faradic stimulation of even a single afferent nerve because of central overlap between that nerve's own constituent fibres.

Therefore among the reflexly excited units of the motoneurone pool there will obtain, and often at the same time, the different grades of excitement, subliminal, maximal and supra-maximal. Altogether, since some of the motoneurones are *not* excited, there are *four* states of the motoneurones, *zero*, *subliminal*, *maximal* and *supra-maximal*.

What then of the gap between maximal and subliminal? Three years ago Adrian and Bronk [8] on the one hand, and on the other Denny-Brown [9], by different methods and independently, succeeded in observing reflex firing in individual motor units. They found rates ranging down to 6 per sec. and 7·5 per sec. in slow extensor muscles, and down to 15 per sec. in the motor phrenic. Now, these rates are not sufficient to secure in their muscle-fibres a complete tetanus; they are not of maximal grade. They are *subtetanic* in the sense of being not sufficient for full tetanus. Different rates, faster and slower, within *subtetanus* grade were observed to occur concurrently among motor units firing in the same muscle [9]. The rates did not correspond with the rate of the break-shock series applied to the afferent nerve [9, 10]. These examples were taken from crossed reflexes; in such there exists of course the internuncial neurone which



A.—Occlusion. B.—Facilitation.

FIG. 5, A.—Two excitatory afferents, *a* and *b*, with their fields of supraliminal effect in the motoneurone pool of a muscle. *a* activates by itself 4 units (α', α, α'' and β'); *b* by itself 4 (β', β, β'' and α'). Concurrently they activate not 8 but 6, i.e., give contraction-deficit by occlusion of contraction in α' and β'.

Fig. 5, B.—Weaker stimulation of *a* and *b* restricting their supraliminal fields of effect in the pool as shown by the continuous-line limit: *a* by itself activates 1 unit; (*b*) similarly; concurrently they activate 4 units (α', α, β and β) owing to summation of subliminal effect in the overlap of the subliminal fields outlined by dots.

(Subliminal fields of effect are not indicated in diagram A.) (Sherrington [15].)

mediates between the afferent nerve-fibre and the ventral horn-cell. In the simple flexion reflex the central connection is more direct, and there the rate of firing of the motor unit shows much closer correspondence with that of the repetitive stimulus [11, 12], at least in some of the motor units and if the repetitive stimulus be not too quick and strong. But even there the motor unit is prone to fire more than once in response to a single centripetal volley [13, 16]. This repetitive after-discharge from a single centripetal volley is still greater in some

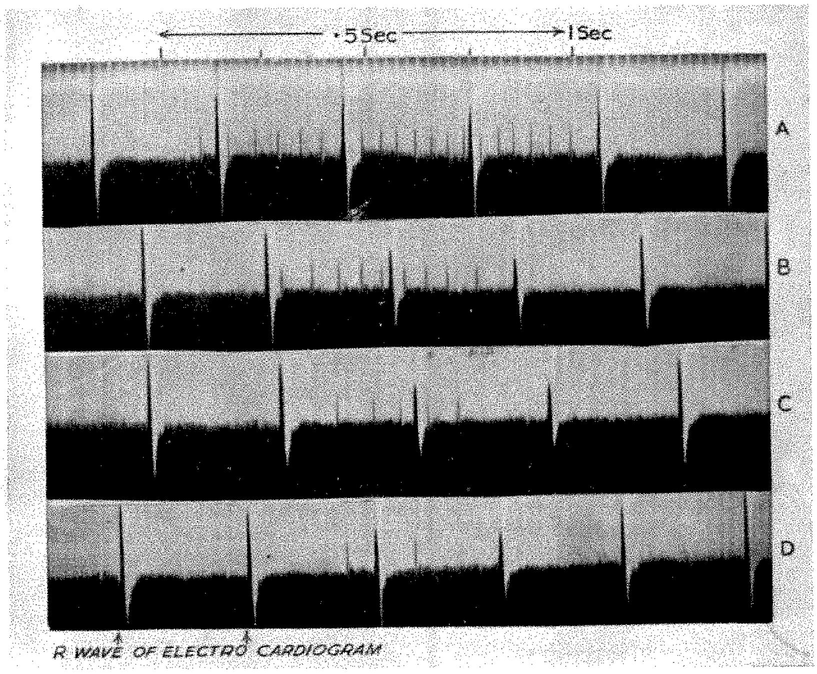


FIG. 6.—Inspiratory firing of a single motor unit of the inspiratory portion (interchondral) of the internal intercostal (cat). A—D : progressive decline of inspiration under luminal and chloroform. The duration of the discharge diminishes and the rate of firing slackens in the successive samples ; A, 27 a sec. ; B, 18 a sec. ; C, 14 a sec. ; D, 6 a sec. (The large waves are of electrocardiogram.) Observation by Professor Adrian, to whose kindness I am greatly indebted for permission to use this unpublished record, a typical example of his beautiful technique.

crossed reflexes and may reach extraordinary proportions. The point here is that often the firing of the motor unit does not agree closely with impulse volleys entering from the afferent nerve. The firing of the motoneurone exhibits a quasi-independence of the rate of volleying of the afferent nerve. This may seem a contradiction of the close correspondence observable in the spinal flexion-reflex under moderate faradic stimulation, but even then the main rhythm tends to be complicated by secondary discharges. Reconciliation of these facts lies in the motor centre being a "summation-mechanism" which takes various summation-times to reach discharging point, and in the neurone threshold itself varying, and with individuality of duration of refractory phase.

Turning from artificial stimulation to natural, we know now, thanks to the discoveries of Adrian and his collaborators, that natural stimulation, for instance, pressure on the foot [14], will no less than does faradic develop its reflex by means of impulse-showers, but these are for the former far more diversely arranged. The trains of centripetal impulses engendered by such "natural" stimulations are not only of different rates among themselves, but vary in regularity, and differ in different fibres with heights of frequency related to intensity of the stimulation at different sense organs, and with different periods of crescendo, and of adaptation and fatigue. The centripetal stream will resemble less a noise than a musical note. This complex inrush, pouring upon internuncial neurones, or directly upon the motoneurone pool, proceeds however from a truly functionally related set of receptors. As compared with the centripetal stream sent in under faradic stimulation of the bared nerve, this natural one will have its impulses less synchronized and in more dissimilar individual trains. It will display consequently richer inequality of excitation on the motoneurone pool. In general correspondence with this (though, since the firing of the individual motor unit may not closely agree with that of the afferent fibre, particular correspondence there need not be) there will result still greater diversity between the firing of individual motor units, inasmuch as the grade of excitement of the motoneurone governs the rate of firing of the motor unit.

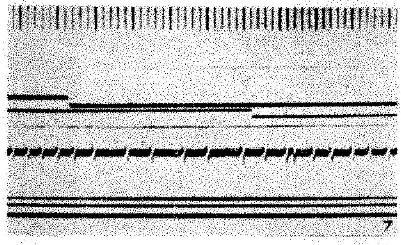


Fig. 7.—Inhibition slackening the rate of firing of the individual motor unit. In *soleus*, decerebrate preparation. A regular stimulus at 50 per sec. to the anterior femoral crossed nerve is continued throughout. At fall of the upper signal a regular stimulus at 65 per sec. to the ipsilateral internal saphenous nerve until the fall of the second signal. (D. Denny-Brown, 1929 [9].)

The rate of firing of the muscle-fibre can be taken as guide to the amount of excitation of the motoneurone. Though there is an intrinsic factor in the rate of response, the quicker the firing the greater the rate of excitation. Thus, in the phrenic nerve the individual motor-fibre fires more rapidly the stronger the inspiratory action (*cf.* fig. 6) [8]; again, in the extensor motor unit firing steadily, weak inhibition [9] by an inhibitory afferent slackens the firing until withdrawal of the inhibition, when the former quicker rate returns (fig. 7).

DEGREES OF ENGAGEMENT OF THE MOTOR CENTRE.

Clearly there obtain under reflex action, and especially with the more natural and less simple, a whole gamut of excitements in the motoneurone pool. Besides the "maximal" (including "supra-maximal") and "subliminal" grades of motoneurone excitement earlier referred to, there will be grades intermediate between those. These intermediate grades, since they produce in their muscle-fibres only imperfect tetani, i.e., "subtetani," may be termed *subtetanic.*

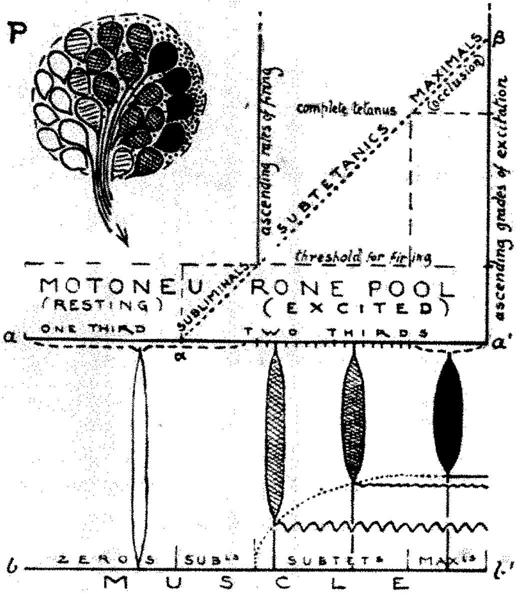


FIG. 8.—Scheme of distribution of excitement in the reflexly activated motoneurone pool of a muscle. Grades of excitement plotted against numbers of motoneurones (abscissa a—a'), and of motor-units (abscissa b—b'); ordinates along a'—β denote grades of excitement in the active fraction of the pool.

The motoneurone pool, P, with motoneurones shaded to indicate different grades of excitement matching different degrees of tetanic construction of their muscle fibres; the lightest shaded motoneurones represent subliminal fringe.

It seems useful to attempt a generalized scheme for the state of a "lowest-level" motor centre of a muscle under reflex excitation. We have to distinguish in it the above broad classes of excitement of the motor units. We may group together as one the maximal and what were styled above the "supra-maximal," and embrace them under one heading, namely, "maximal," because of their like effect in respect of contraction tension. The broad classes are then three, "subliminal," "subtetanic," and "maximal." There will be in addition a zero class where the excitation is nil. In the accompanying chart the grades of excitement and the rates of firing ascend the ordinate scale. The rate of excitement is greatest where in the centre the successive arrival of converging impulses is quickest and thickest.

First, as regards weak reflexes; since a central excitation field reduced to its minimum is entirely subliminal [15, 16, 7, 5], clearly in weak reflexes the subliminal fringe will constitute a larger proportion of the excited field. This has been often observed.

As regards strong reflexes; in them excitement of the "maximal" class embraces in certain exceptional examples the motor units of a whole muscle [5]. Often in strong reflexes "maximal" motor units are plentiful enough to include all of the motor units engaged by a weaker reflex [5]; this latter's contraction tension can then be entirely concealed by that of the former.

ADJUSTMENT TO CHANGES OF EXCITATION.

Reduction of the stimulation of the afferent nerve means excitation of fewer fibres in it. The field and density of the exciting central terminals is thus reduced. This reduction may fall heavier on one class than on another. But let us suppose it more general and more equable. Let us suppose, in the accompanying chart of the reflexly excited motoneurone-pool of a muscle, a general withdrawal of excitation such as to reduce existing excitements by a given, say the just subliminal, amount. We may sample this withdrawal for its effect motor unit by motor unit along the scale of excitation of the chart. The total result is a decrease of contraction which is traceable to several factors. One consequence is that line α—β rises from the abscissa less far to the left; that is, the total excited field somewhat shrinks. The old subliminal fringe drops out of action altogether to be replaced by another, in this case not less plentiful, supplied from former "subtetanics." All along the firing line the fire, as examined motoneurone by motoneurone, somewhat slackens. Units well up in the "maximal" class continue to give the same contraction-tension as before; other "maximals" lower down degrade into the subtetanic class, and yield less tension. In the subtetanic class all slip lower, yielding individually less tension, and some cease to discharge, entering the subliminal fringe. In records where two motor units are firing, one somewhat faster than the other, it can be seen that when the faster slackens somewhat its slower companion may disappear altogether, i.e., will cease firing. An excitation causing the remaining one to quicken again restarts the companion which had stopped. The waning and waxing affects the two and in the same direction, and what will slow one will stop the other. Sometimes, however, one unit will persist unaltered although another stops.

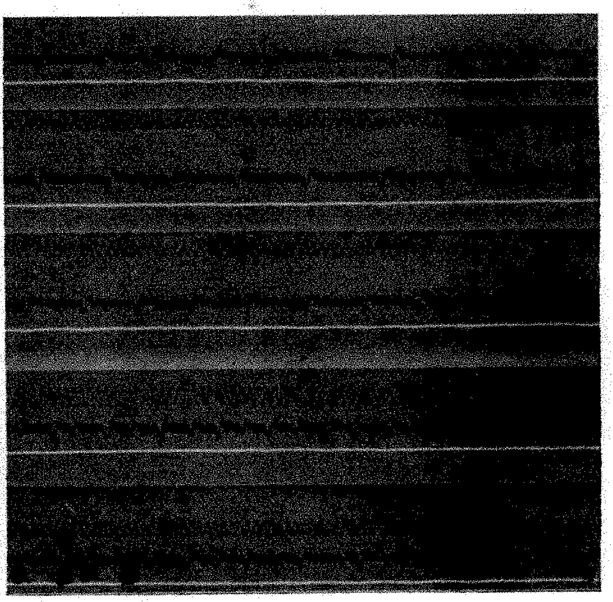


FIG. 9.—Example of consensual behaviour of two motor units α and β in decerebrate *soleus*. In the lowest record α and β are both firing under crossed excitation (of 50 per sec.) at rather slow rates, β rather faster than α. In the next record above both are rather quicker. In the fourth record, the quicker unit β is much slower than it was earlier and α has ceased to fire. (Eccles and Hoff.)

On occasion some units are increased in excitement while others are reduced. This happens under conditions, however, which do not preclude inco-ordination; namely, the stimulation of an afferent nerve which tends to produce some ipsilateral extension and some ipsilateral flexion mixed. A likelier field for search might be higher level co-ordination, such as Dr. Blake Pritchard [17] has been investigating. Though even here there can be quite fractional inhibition

But the outstanding instance of shift of the individual unit along successive grades of excitement in the course of a single reflex is the instance of which, thanks to Adrian and his co-workers, most is known, namely, that which as they have shown characterizes the opening phase [10] even in these "lowest level" reflexes, especially, we may suppose, when evoked by "natural" stimuli. The firing of an engaged motor unit then opens at slow rate and runs a gradually, though it may be rapidly, ascending course to reach a climax frequency. The reflex, in short, even as regards the excitation of the individual neurone, develops gradually. This contrasts with the spinal flexion reflex as exhibited under faradization of the bared afferent nerve. The latter with characteristic abruptness develops its full tetanus at once. This d'emblée opening [18] is but in agreement with the form possessed by the stimulus which excites it; that stimulus tetanizes at once and at its full rate all the afferent fibres it is going to tetanize. More remarkable is that the crossed extension reflex under similar stimulation does not so respond but opens gradually [18], showing both "recruitment" and acceleration of individual firing [10], often after a marked period of *addition latente* [19]. The rate of recruitment is accelerated by strychnine, for as shown by Bremer and Rylant (1926) strychnine shortens the fundamental reflex latency [56].

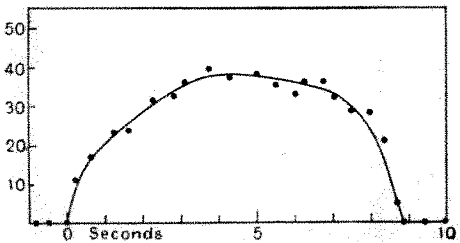


FIG. 10.—Curve showing frequency of impulses per sec. in nerve fibre to *tibialis anticus* during a flexion-reflex. Decapitate preparation. (Adrian and Bronk, 1929, [10]).

Doubtless these features have relation to intermediation by a relay neurone. But the d'emblée opening may be regarded as "artificial," in the sense that few "natural" stimulations are likely to produce it. Cutaneous or proprioceptive stimuli are not easily imagined which will develop their height "rectangularly" and with the suddenness of a faradic current on an afferent nerve-trunk. In the flexion-reflex excited by the "natural" stimulus of pinching the foot, Adrian and Bronk [10] show the rate of firing of an individual motor-fibre to begin at a low rate, gradually reach its climax and gradually decline. Their instance slowly ascended the subtetanic scale during the course of some 4 sec. and never acquired "maximal" grade. With the crossed extension reflex evoked by mechanical stimulation of the opposite foot, they traced a sample individual unit opening firing at a rate low down in the subtetanic scale and rising steadily in rate to enter the "maximals" group (60 per sec.) in about 5 sec. Adrian and his co-workers furnish many examples which show that one and the same motor unit climbs through successive grades of excitement in the opening phase of reflex response. In our generalized chart schematizing the grades of excitement in a motor centre and their distribution, we may picture the individual unit at beginning of a natural reflex as starting somewhere low down in the subtetanic grade and then climbing to take a more settled place in, if the reflex be strong, the maximals. In short, for the opening phase of a simple reflex we picture line *a β* (fig. 8) emerging from the level of the base line (the quiescent pool) and gradually rising, becoming tilted as it does so, to assume a height, slope, and extent varying with the "strength" of the particular reflex. In occasional strong reflexes, as provoked in the laboratory, we know that the whole of *a*—*β* comes to lie above the topmost subtetanic level, i.e., within the "maximals," and that *a*—*β*'s horizontal extent may then be coterminous with the whole abscissa. On the other hand, we know that in certain weak reflexes the whole of *a*—*β* lies below the lowest tetanic level, and that *a*—*β*'s horizontal extent is then relatively short.

The terminal phase of the reflex, when caused by simple withdrawal of the exciting stimulus without complication by inhibition, we may picture as an extension of that weakening already dealt with above, and again with its abruptness softened, especially for strong reflexes, by the protraction of individual after-discharge.

The important and fascinating discoveries of Adrian and his collaborators seem thus to supply a paradigm of the course of discharge of rhythmic reflexes in general. If a natural reflex act exhibits gradual development of its drive of the motor unit, and if similarly the subsidence of that drive be likewise gradual, as we know from after-discharge it is, each alternating phase of a rhythmic train of action (respiratory ventilation, stepping) will in effect be just a waxing and waning of the frequency of discharge of certain individual motor units periodically repeated. The observations of Adrian and Bronk indicate that the grading of contraction of the rabbit's diaphragm in inspiration is effected mainly by grading the frequency of the firing of the motor unit with little "recruitment" at all. The deeper inspiration means in that case quicker and more prolonged firing of many of just those same motor units which in shallow inspiration fire less rapidly and less long. The resemblance between spinal "stepping" and respiration is close in many respects [20, 21]. The tetanic outburst rhythmically repeated in the spinal scratch-reflex is more abrupt and more brief, e.g., $\frac{1}{9}$th sec., and is less amenable to grading in rate.

ADJUSTMENT BY SUBLIMINALS, SUBTETANICS AND MAXIMALS RESPECTIVELY.

Thus, then, each of the broad grades of excitement of the motor centre contributes to active adjustment of the reflex contraction, and contributes somewhat in its own way.

Subliminal fringe adjusts mainly on the basis of extensity, increasing or diminishing the total number of motoneurones engaged. It, so to say, mediates between excitation and the quiescent pool outside. That this is so is shown by the *addition latente* [19], and recruiting opening of the crossed extensor reflex, and is to be inferred also from the gradual course of the development of excitement shown by Adrian and Bronk for the individual unit at commencement of various reflexes. The fringe recruits from the quiescent pool; back into that pool it sheds. It also, of course, feeds the supraliminal field. Its relation to this latter is sometimes illustrated under conditions strikingly simple. Thus, to take a particular case [22]:

Two similar volleys fired into a flexion centre in quick succession. The first excites a reflex twitch in 70 motor units. The second, following quickly, finds those 70 motoneurones refractory because they have just fired. But in 45 other motoneurones which the first volley excited, though not to the extent of firing them, the second volley finds still some subliminal excitement left by the first, and, itself subliminal for them, yet adds an increment of excitement sufficient for their firing; the myograph gauges their number from their contraction. The exciting volleys are then strengthened, so as each singly to fire 180 motor units instead of 70. But these two stronger volleys in sequence discover little fringe. Therefore evidently the 45 subliminals of the weaker reflex must have become some of the 180 supraliminals of the stronger. In such an experiment, the summation being confined to two stimuli, opportunity for revealing the whole fringe is small.

Temporal summation by its mere iteration possesses powers less limited than spatial summation can attain alone.

Subliminal fringe is absent in some strong reflexes, at least as concerns a particular muscle. That is not to say it is absent *altogether*, for a reflex employs concurrently several synergic muscles each with opportunity for fringe [23].

The large fringes of weak reflexes are an effective factor for co-ordinative liaison and combination between such reflexes, and between them and others. Thus, nothing is more frequent than in the course of an experiment with, for instance, the ankle extensor attached to the myograph, to see, if head and neck be passively turned into the so-called favourable position, the same limb stimulus evoke a much greater reflex than before, even although the new posture of the head and neck evoked itself no reflex from the muscle [24]. An individual motor unit, sampled for observation, then beats faster than before; on replacing the head and neck in the less favourable position the motor unit fires less quickly again. The facilitation from above is largely, and may be entirely, subliminal and upon it summation builds, when the local reflex is repeated. Subliminal reflexes impinging with allied effect on the muscle can produce large quantities of contraction [7].

Thus again with Rademaker's [24] supporting reaction from the sole of the foot and the soleus postural stretch-reflex. Also with Bremer's [26, 27] cerebellar influences upon the extensor reflex of the limb; and these remind us that there can be inhibitory fringe as well as excitatory, and that its withdrawal can give Hughlings Jackson's "release," as luminously expounded by Sir Henry Head. It is mainly by subliminal fringes of excitation that the higher nervous centres exert the postural adaptations which are as necessary to the animal as is posture itself. Destruction of the rostral cerebellar cortex (Bremer [26], Rademaker [28]) suggests itself as accounting, by removal of reciprocal—and especially inhibitory—fringe from limb antagonists, for the dysmetria—and hypermetria—observed as a cerebellar symptom.

The subtetanics group.—An important attribute of these is their power to grade contraction. Rate of firing of the motor unit grades contraction by so spacing the successive contraction-waves that the integrated tension falls variously short of full tetanic. The shortage is of course greater the slower the wave-succession, and the scale of grading becomes progressively less open as full tetanus is approached. A given increment of frequency of firing of the motor unit represents less increment of contraction-tension in proportion as the frequency of firing in the motor unit is already high; until at last it represents no increment at all (occlusion) [5].

The subtetanic contraction of the individual motor unit is of course tremulous. I suppose, therefore, the weak reflex will contain more tremor, but I do not know that myographically. With a power-unit like that of gastrocnemius, which averages a contraction-wave of some 9 g. [3], its tremulous contraction must threaten the steadiness of the whole muscle. But lessening such defect is the circumstance that the various subtetanized units are out of phase one with another. Individual differences of rate of summation of excitation and of duration of refractory phase will tend to keep them so. If a number fall into step tremor must become gross.

Denny-Brown has brought forward [9], and supported from his experiments, an interpretation on this basis of the clonus readily induced in the decerebrate preparation of the laboratory. There, he says, clonus arises simply from the tonic normally asynchronous discharge of the units becoming synchronized. The tonic stretch-reflex of the laboratory can exhibit in the firing of its units all shades of transition between asynchronism and complete synchronism, and it can be made to pass from one to the other reversibly by suitable conditions of initial pose (Viets [30]), and, as Pritchard [31] has particularly shown, of tension. Conducive to the position taken by Denny-Brown [32] is his interpretation of the "silent period" of the galvanometer string following a knee-jerk as an inhibition, derived from the proprioceptives of the muscle itself and evoked by the jerk itself from its own muscle. This inhibition damps the discharge of the jerk down in effect to one centrifugal impulse. Fulton [54] argues the pause a lapse of excitation. In clonus the motor units get into step as regards contraction, and their keeping in step is accentuated by their pauses keeping step likewise. Their beats in the clonus are punctuated by their proprioceptive pauses forming a vicious circle keeping them in step.

Inherent in the operation of the subtetanic motor units is, besides tremor, some waste work, an uneconomy which has been dealt with by Bronk [33]. Can we be sure that nature is in love with economy? In this instance the uneconomy seems more than offset by the advantage gained in delicacy and range of means of grading reflex contraction strength.

The "maximals" group.—In weak reflexes, for instance in weak postural reflexes, there may be no "maximals" at all. A weak tonic postural reflex of *soleus* (cat), favourable to isolated examination of single motor units, not rarely fails to exhibit a single unit firing in other than subtetanus. On the other hand, in strong reflexes there may be none but "maximals" in the entire motoneurone pool of a whole muscle [5], as driven in laboratory experiment; though this is quite exceptional. In the "maximals" group each unit yields its maximal contraction. Motor units added mean added contraction, and removed mean contraction lessened. All additional excitement received here lays aside its mechanical equivalent. That is to say, "occlusion" occurs here and is therefore prominent in strong reflexes. It is the "maximals" group which by its growth limits more and more the further increase of the reflex muscular response. It brings into the relation between increase of reflex contraction and increase of reflex stimulation some resemblance to the approximately logarithmic ratio holding between increment of sensation and increment of stimulus. The maximals are economical in a sense, because contraction-tension is maintained at a smaller expenditure of energy in a stronger contraction than a weaker.

I would not pursue this subject to tiresome length. We arrive at this: that the motor centre—old but expressive term—is not a mere passive relay on the path out to its muscle, nor merely a place of passive assembly of impulses converging upon the muscle. The motor centre grades the excitation of the individual motor unit, causing its faster or its slower firing. The motor centre is a central instrument which adjusts *actively* the contraction-strength of its reflexes; it works on the basis of the "central summation process" [15, 16]. Driven and fed by centripetal impulses, it deals with them on the summation basis. It is in short a "summation-mechanism." It operates on the individual motoneurone by excitation-summation; in that way it can exert a whole scale of degrees of excitement upon one and the same individual motor unit, firing it faster and so obtaining nearer full tetanic value of contraction, or slower with greater defect from full tetanic contraction. It also shows changes in extensity with variation in the number of motoneurones. Yet, since central impulses in order to excite a motor unit must be summated, the central mechanism is ultimately wholly a summation apparatus. One secret of its co-ordinative power lies in its power of summating with almost negligible time-lag shifting fringes and mobile shades of excitation that meet and overlap upon it. These join and disjoin, expand and shrink, as afferent channels leading from various sources come into or drop out of action;

and each and every time the central apparatus subjects them to or releases them from its summation.

The motoneurone which this central summation drives reacts in several respects as Adrian has shown a receptor to react. A difference is however its more prolonged maintenance of the rate of firing under persistent stimulation, i.e., its greater resistance [15] to fatigue and "adaptation." It does not run down so quickly as do most receptors. Moreover, the central summation mechanism develops a greater range of intensities both upward and downward than the muscle-fibres which it operates can with their tension follow. If this seem wasteful of central activity, we may remember that additional excitation exerted on a motor unit, already driven "maximally" for tetanic contraction, is not necessarily wasted. That surplus remains still a contribution to co-ordination, because further excitation offers a further resistance to inhibition [34, 35, 36]. Just as an added inhibition in the case of an already quiescent neurone although in one sense wasted is a further protection, which co-ordination may need, against excitation. In times of crisis the dilemma lies between strong actions, and the very strength of the action taken may serve to safeguard it from extrinsic interruption.

CONCEALED REFLEXES.

Quantitative adjustment of amount of contraction seems to first thought of purely quantitative significance. Yet, since strengths of contraction may affect and shift the scope of an act, contraction-strength can acquire qualitative value. The laboratory plan of obtaining reflexes by direct stimulation of bared afferent nerve is for some purposes essential. It is however artificial and certain reflex artefacts derive from it, among them this, that each large afferent nerve presents a dominant reflex which may conceal other reflexes. This dominance is itself a compromise, although often an overwhelming one, between conflicting reactions. To display natural reflexes thus submerged we have to turn to localized stimuli natural for them. In this way can be traced the otherwise concealed ipsilateral extension reflex of the limb. Its broad quantitative course seems rather different from that just considered.

It activates the great extensors of the limbs. It is a reflex included in that complex which works the limb as tool for locomotion and for standing. When, in reflex life, the animal reacting to the geotropic organ in the head (the labyrinth) has been set on its feet, its limbs are by that very fact saddled with its weight. The extensor reflex of the limb becomes then an anti-gravity reaction. *Per se,* it is not so. Just as the hind limbs of the spinal dog when passively put upright "stand" [20] by reason of the superincumbent weight then eliciting the postural extensor stretch-reflex, so in like manner the ipsilateral extensor reflex, although not itself specifically geotropic, becomes then an "upstanding" reflex adjuvant to geotropism. This upstanding reflex in dealing with its habitual burden, the body-weight, exhibits several grades of strength. Each grade is adapted to a particular form of the "upstanding" act and behaviour. The weakest is that adapted to "standing"; there all that is wanted of the great extensors is to support their load to the extent of preventing their limb from sinking under it. This grade of the reflex is postural. It is as regards the great extensors at knee and ankle essentially the static stretch-reflex; with, preparation permitting, some fringes of support from neck and labyrinth. The motor units it employs in the great extensors are, conformably with its mild contraction-strength, a small proportion only of the total aggregate composing these muscles. But this small percentage is not a diffused and scattered population, it is a segregated set which forms at the ankle the *soleus* part of the great calf muscle, trespassing little into the gastrocnemius [9]. At knee it forms similarly the *crureus* and adjoining *vasti* and spreads little into *rectus.*

Turning to the stronger forms of this same "upstanding" reflex, these extend its scope from mere static support of the limb to propulsion of the body; they are locomotor. The extension of the limb then takes the form of the extensor phase of the step. With increasing grades of strength and speed this reflex transcends walking and running and becomes the gallop. All of these several forms are represented spinally [20]. The spinal gallop is well observable in the dog, when after a cervical spinal section the "shock" period is over. Harmless pressure applied to the plantar pads, even of a single hind-foot, will then evoke the extensor thrust in all four of the limbs together [20]. The brief backward thrust of the hind-limbs is accompanied by a similarly timed outreaching thrust of both fore-limbs forward. The picture presented by the reaction even as the animal lies on its side in the stall is unmistakably the extension phase of the gallop. It is followed in all four of the limbs by brief active flexion of each limb. In this "extensor thrust" of the gallop the gastrocnemius can be felt and seen to be actively involved, and at the knee the contraction, quite differently from the postural reflex, spreads far beyond crureus.

In short, this ipsilateral extension reflex which the labyrinth system impresses into geotropic service for an "upstanding" limb, exhibits a quantitative grading somewhat different from that of the prototype muscle-centre we envisaged earlier. In these great extensor muscles the "upstanding" reflex as it grows in strength and changes its functional scope passes over from the restricted field of slow red-muscle motor-units to large reserves of quick pale-muscle motor-units which are in fact the main masses of these large extensor muscles. These latter motor units are, to judge from gastrocnemius, individually more powerful than those of the red kernel muscle *soleus*, thrice as powerful [3] and nearly thrice as rapid [37, 38].

Thus, the majority of the extensor units at ankle and knee appear as antigravity units held in reserve for such work as the run, the gallop and the jump. At ankle, in the cat, some 1,100 stronger units held in reserve behind 230 weaker ones. In contraction power the reserve is very high. Thus, isometrically measured at the ankle in a 3·5 k. cat, 35 kg. of reserve contraction; at ankle and knee together and for both hind-limbs an isometric contraction-tension of some 170 kg. for a 3·5 k. cat [39]. In its quantitative grading the reflex seems to extend its grasp from slow-contracting, less powerful and in a sense more economical motor units to more rapidly-contracting, more powerful, in a sense less economical units for more occasional use.

We are fortified in tracing this "upstanding" reflex through its graded scale, from weak to strong, as a single functional entity, since there is no ground now for regarding the postural contraction or tonus as a contraction essentially different from that of other forms. It is the same rhythmic process but at slower rate. This slowness may account for a difference which has sometimes been thought qualitative between postural or tonic and other contraction, namely, relative exemption from fatigue. The relative slowness of firing may of itself account for that. Slow firing of the motor nerve, as experiments by Lady Briscoe [40] demonstrate, avoids and even allows recovery from fatigue, which faster firing induces rapidly.

The importance of posture is emphasized sometimes by saying that it is the starting-point and the end-point for every movement. But posture, as Ramsay Hunt remarks, accompanies "movement like a shadow" [41]. Stanley Cobb writes [42] that "they coalesce and often cannot be separated." An apt illustration, familiar in the laboratory, is the posturing of the spinal scratch reflex. The artificial flea in the form of a faint faradic current is applied for instance to the skin behind the ear. This electric tickling excites the reflex, probably through the superficial nerve-endings round the hairs, for after shaving the skin the reflex is difficult to get [43]. The same side hind-foot breaks out into its scratching, a rhythmic movement which involves digits, ankle, knee and hip. Alongside this movement and just as much a part of the reflex, is posture [44], a maintenance of flexion of the limb as a whole, along with a steady incurvation of the body toward the stimulus side, the neck deviated and the head partly turned back, so that the foot more readily may reach it. All these are quite steady reflex postures. *Some* of the muscles actually engaged in the rhythmic movement seem engaged in posture as well as in movement, posture and rhythmic contraction together in the same muscle. The posture not merely alternates with the movement but accompanies it and dovetails in with it. Our earlier schema of a reflexly excited motor centre pictured the motoneurone pool as that of a single muscle; but even the simplest flexion reflex excites several muscles, and from threshold up. Lorente de No [45], recording graphically the contractions of the individual eye muscles, shows that every labyrinth reflex acting on the eyes employs all twelve muscles together. With the flexion reflex of the limb excited from any efferent nerve of the limb, the flexion is plurimuscular from the very outset [23]. Thus, with a small digital nerve at minimal stimulus the muscular response starts simultaneously in ankle-flexors and knee-flexors and hip-flexors together, and so on. Thus, from the point of view of the spinal reflex, a motor-unit in say *tibialis anticus* has closer functional alliance to some in *semitendinosus* and *tensor fasciæ femoris* than to many of the fellow motor-units in its own muscle. The simplest spinal reflex, as Hughlings Jackson was wont to insist [46], "thinks," so to say, in movements, not in muscles.

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The tiny skin spot stimulated in the spinal scratch reflex brings into action a whole array of muscles. In the spinal cat, a wholly insentient preparation, they can be freely laid bare and examined in their activity. Without exhaustive search we soon reach thirty-six [44]; nineteen in rhythmic action at five beats a second, seventeen in steady, i.e., postural action. The rhythmic beat is a brief tetanus lasting about $\frac{1}{5}$ sec., followed by a quiescence sometimes long enough for complele relaxation from the tetanic beat. The rhythm is not generated in the cutaneous nerve-ending—the hair-endings—for it occurs on faradizing at other rhythms the afferent nerve itself, and indeed quite easily by electrical stimulation applied to the cut cross-surface of the top of the spinal cord itself [47]. Nor is it a rhythm developed, as was suggested above for clonus, by a retropulsive effect

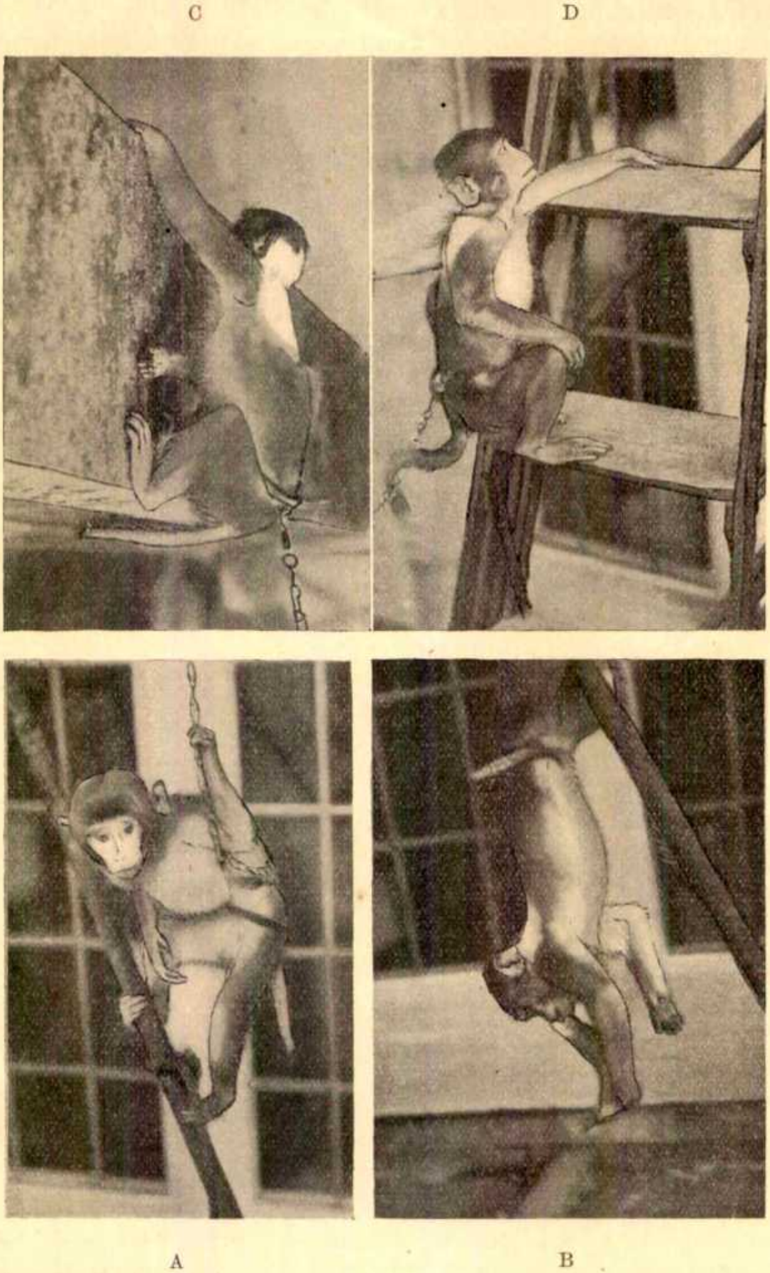

FIG. 11.—*Macacus rhesus*, in which the posterior roots of the 5th, 6th, 7th, and 8th cervical and 1st, 2nd and 3rd thoracic nerves of right side had been severed intradurally nine days earlier. Limb is not used, and has been unused for a week under ordinary circumstances (figs. A, B and D). On exceptional occasions, e.g., under excitement, the arm is attempted to be made use of, but is wildly misdirected (fig. C, in attempt to climb parapet wall). Stimulation of the corresponding motor cortex detected no impairment, even in the finger movements, as electrically evoked from cortex and compared with normal side. (Denny-Brown and Sherrington.)

from the operating muscles themselves; that is clear, because the reflex persists after the whole of the scratching limb has been desensitized by severance of its posterior nerve-roots. The rhythm is clearly of central origin, with its seat in the hind-limb region of the cord. It is not easy to say what tunes such a rhythm, since it is *not* timed by the periphery as in a *clonus*.

The scratch-reflex does not stand alone in this unexpected independence of actual local peripheral reflex guidance. It is noteworthy that "scratching," "stepping," the "pinna reflex," the "shake reflex" are not elicitable seemingly by any stimulation of the cerebral cortex. They are, however, exaggerated after destruction of the cortical "motor area."

It is surprising to find the movements evoked by stimulating the motor area of the cerebral cortex not obviously impaired by complete desensitization of the limb itself. Willed movements are upset in the extreme. In the monkey the desensitized limb is practically useless, for prehension quite so. The animal soon treats it as useless and as an encumbrance worse than useless; it attacks it and would tear it away. Yet, when the motor cortex is examined by electric stimulation, not only does it evoke in the deafferented arm and hand the customary movements just as readily as usual, but those movements reveal no obvious departure from their usual co-ordination. They can be compared with the movements evoked by corresponding cortical stimulation in the normal fellow-limb and reveal no abnormality. It seemed so to Mott and myself [48] in our observations now long since. It has seemed so again to Dr. Denny-Brown and myself, applying recent myographic and galvanometric technique to sample muscles. Wild inco-ordination under willed action; little or no abnormality under the action of the directly stimulated motor cortex. A striking contrast. One may relate it to the probably very direct play of the pyramidal tract upon the motoneurones [49, 50]. It is a *caveat* against accepting the movement excited electrically at the motor cortex as any close homologue of a willed one. It seems as unimpaired by desensitizing its limb as is the spinal scratch reflex itself. Thus, too, an elemental difference is revealed between the clonus of rigidity, e.g., decerebrate rigidity, and the cortical post-stimulation clonus, the Jacksonian epileptiform. The latter is not affected by deafferenting the muscles or indeed the whole limb; the former is of course entirely annulled. The intact proprioceptive "circle," which is a factor essential for the one, is quite inessential for the other.

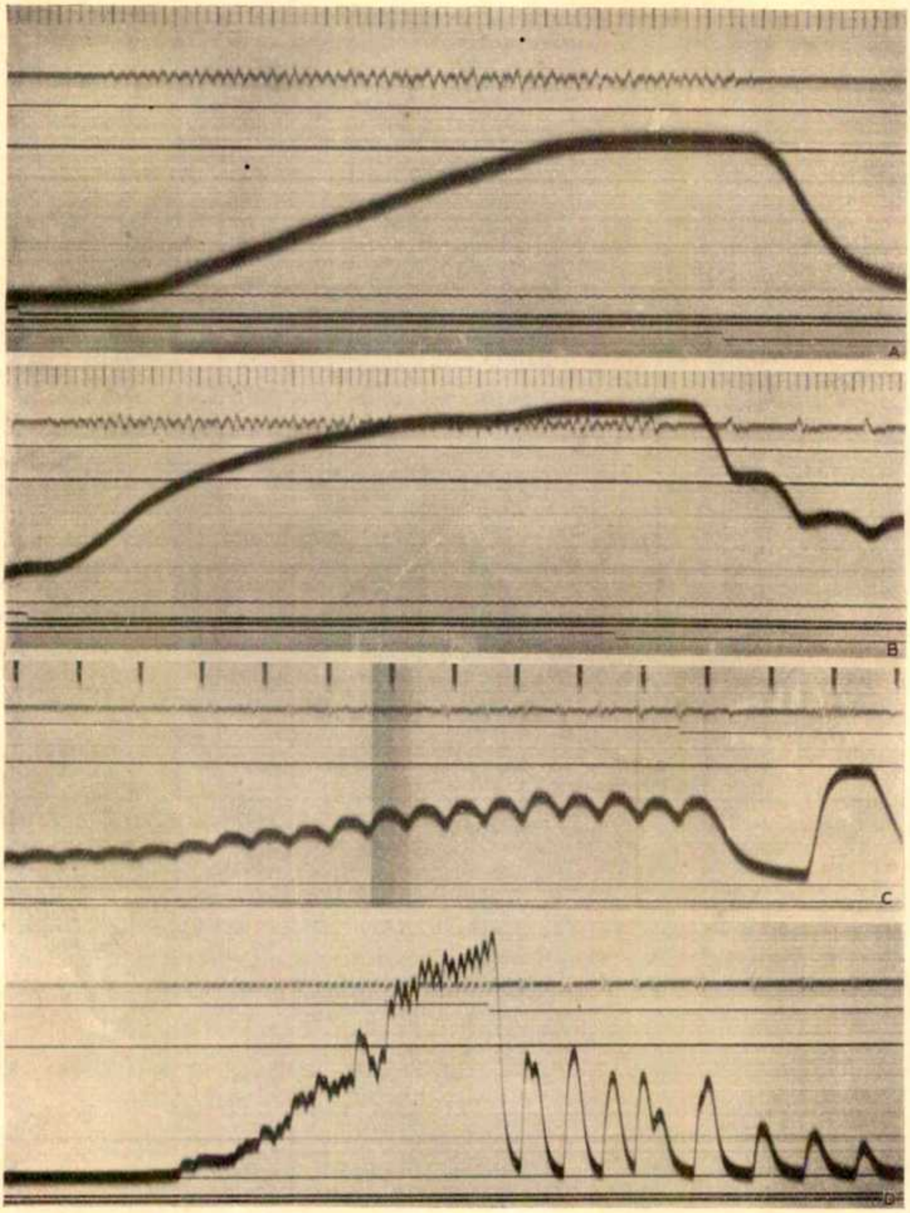

FIG. 12.

(For description see foot of next page.)

A somewhat similar state of things exists in respect of the stepping reflex; so much so that Graham Brown [21] argues, from many observations, that the stepping is a centrally initiated and executed cyclic reflex essentially independent of—although modifiable by—peripheral stimuli. It certainly often occurs quite in absence of all plantar or foot stimuli, for instance, in the air or with all four feet wholly desensitized, *cf.* [20].

FARADIZATION OF SPINAL TRACTS.

As with scratching so with stepping, the reflex can be excited by weak stigmatic unipolar faradization from the cut transverse face of the spinal cord [47] at a tiny area in the lateral column, the stepping being for instance in the hind-limb and the point stimulated at the top of the cord, the preparation a decapitated cat. The scratch reflex will not alter its rhythm under either peripheral or central stimulation, i.e., from cut face of cord. But with stepping the weak faradic stimulus excites in the hind-limb of the same side stepping which from walking becomes running as the stimulus is made slightly stronger. It tends to be accompanied by feebler stepping of the opposite hind-limb, agreeing in rate with that of the fellow-limb but oppositely timed so that it

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FIG. 12.—The four records are from contractions of the right flexor profundus digitorum of a *M. rhesus*. The 5th, 6th, 7th, 8th cervical and 1st, 2nd and 3rd thoracic, dorsal roots of this animal, were severed intradurally on the right side, under deep anæsthesia, and a recovery allowed of nine days before the animal was again anæsthetized, the left motor cortex explored, the muscle prepared and the following records made.

The motor cortex was stimulated by a unipolar electrode with the indifferent electrode attached to the left hind limb, and the stimulating current was a series of break shocks at the rate of 50 a second, delivered by a torsion wire key. The onset and cessation of the stimulus series are each shown by the fall of a short circuiting key, the movement of which causes a step in a line on the record.

A. The onset, plateau, and termination of a contraction. The onset of the stimulus series is marked by the step in the third line from the bottom, and the cessation of the stimulus is marked by the step in the lowest line on the record. Rate of stimulus marked by rippled line in lower part of the record. Regular waves at 50 a second appear in the action currents Time marked in vertical strokes at 1/50 sec. intervals.

B. Similar to A, but showing the onset of clonic after-discharge in its usual form.

C. The contraction in response to slowly repeated single break shocks to the motor cortex (8 a second); beginning about six seconds before the record was made. The cessation of the stimulus series occurs at the fall of the line just below the galvanometer string shadow. To show the separate mechanical contractions in response to each break shock stimulus, and the gradual development of secondary action current waves accompanying the discharge provoked by each stimulus. The first beat of epileptiform after-discharge is also shown and is typical in every way of a common type of after-discharge in the normal contraction. Time marked in vertical strokes at 1/5 sec. intervals.

D. Response of long, latency (summation time), produced by a slow series of break shocks (8 a second), and with rhythm of the stimulus showing in the mechanical record. The cessation of the stimulus (at step in upper signal line) is followed by a clonic after-discharge of slow rhythm. Time indicated by the rhythm of the contraction response, which corresponds with that of the stimulus at 8 a second. (Denny-Brown and Sherrington.)

alternates in phase with it, as in natural locomotion. By arranging two electric circuits two stigmatic electrodes can be used with separately adjustable strength of stimulation. If then the right and left points are stimulated concurrently on the cut face of the top of the cord, a subliminal stimulation of one is found to become effective on applying a subliminal stimulus to the other. Galloping can be obtained by stimulating the two points concurrently with somewhat stronger stimuli. This stepping point lies in the deep dorsal part of the lateral column. If, while the stepping is in progress under excitation of this point, a weak stigmatic faradization be applied to the ventral part of the ventrolateral column (probably vestibulo-spinal tract) of the same side, the stepping at once slows down or stops. Stimulation at this point when the dorsolateral point is not being stimulated gives extension of the same-side hind-limb. The dorsal point I mentioned as the "stepping" point; the ventral point might be called the "standing" point. As yet I have examined it only at the above-mentioned level. The right and left ventral column points when concurrently stimulated reinforce each other. The observations occur equally well with the stepping limb suspended, that is, with the proprioceptive stimuli in the stepping limbs quite otherwise than when the limb is bearing superincumbent weight, also quite without plantar stimuli, the feet being in the air. This complex cyclic act, with the various timings of its sequence as initiated and maintained by excitation of a slender channel descending into a spinal lumbar region from above, seems strangely independent, for guidance rhythm or support, of local centripetal factors in the limb itself. Stimulation at the stepping point in the lateral column starts the limb stepping and keeps it going practically at what pace it likes. Stimulation of the antagonistic descending path slows the stepping and if stronger stops it and changes it into standing. With stepping and standing as incompatible opposites this instance where the reaction deals with the limb on large lines, and suppresses one of two incompatible reactions in order to bring in the other, offers analogy to reciprocal innervation. It further illustrates a feature of co-ordination which I have insisted on elsewhere; namely, that for a muscle or a muscle-group to be contracting does not exclude its being under inhibition. Let us glance back, for instance, at our generalized picture of the excited motor centre, and take it a stage further by inserting some inhibition. We see at once that the inhibition counteracting according to its degree less or more of the excitation, can slacken or stop the firing of some or all of the discharging motoneurones. Only in the extreme grade which stops all the motor units will the inhibition reveal itself as a complete absence of contraction of the muscle or muscle group.

CONCLUDING REMARKS.

I must not detain you longer. I would only remark that the present time seems of unusual promise for neurological investigation, both in the clinic and the laboratory. I think the same feeling informed the penetrating and suggestive lectures given not so long since by Dr. Walshe [51]. The advent of possibilities of sampling the individual nerve and motor unit opens out opportunity for advance. The centre's activity, which for too long has been only a statistical quantity, can yield up some secrets of its precise individual activities.

If then the present offer enhanced promise for neurological investigation, it is a time which for that reason calls for close liaison between them. For effective co-operation one essential condition is that clinic and laboratory lie near together. The laboratory in a word has to be on the spot. Apropos of this, if I dare think aloud, a reflexion is natural on this occasion. Where in all the world could be more fitting a point for such liaison than at the Institution, which, with its noble tradition of teaching and research, enshrines within its portal with peculiar right the bust of the great master to whom our lecture to-day seeks to pay commemorative tribute, Hughlings Jackson.

I have dealt very imperfectly with a small bit of a large problem. I have kept much within the purely experimental laboratory. The smallness of the fragment is disappointing. The problem itself has the interest that, large as it is, it yet—to speak *more Hibernico*—is larger still. Hughlings Jackson, in his writings, turns back and forth between muscular co-ordination and mental experience, as if for him they were but aspects of a single theme. It may be that to decipher how nerve manages muscle is to decipher how nerve manages itself. If so, not without significance should be what we have just glimpsed, that there are in the nervous system heights of excitation and depths of inhibition higher and deeper and with grades of adjustment ampler than muscle with all its subtleties can commensurately express.

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THE PHYSIOLOGICAL INTEGRATION OF SENSORY PROCESSES WITHIN THE GREY MATTER OF THE NERVOUS SYSTEM: A CRITICAL REVIEW.

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INTRODUCTION.

It is common knowledge that sensory impulses do not pursue an uninterrupted course from the endings in which they originate to the sensorium. All paths ascending to the cerebral cortex traverse grey matter at least twice before they reach their destination and involve chains of at least three neurones. The function of these synaptic connexions in grey matter has been little discussed; they appear frequently to be regarded as no more than relay stations in which impulses are transferred to a new set of nerve-fibres. A moment's reflection shows that such a view is totally inadequate and provides no explanation of their existence.

Among those who have ascribed more definite functions to them, Sir Henry Head is especially worthy of mention. In his important work on the regrouping of impulses in the central nervous system, he elaborated the crude theory of impulses being relayed, by supposing that individual neurones of the higher level gather up impulses subserving some specific quality of sensation irrespective of the precise origin of those impulses. He and Thompson wrote in 1906 [36, p. 405]: "It is as if the gallery of a concert hall were fitted with a series of resonators, each of which was tuned to a certain note. Each resonator would pick up a peculiar tone, whether it was produced by the strings, the brass, or the wood-wind."

Head has further consistently advocated the view that integration of another kind is brought about at these places, and has pointed out the facilities which they offer for interaction between various trains of impulses. On the one hand, combination or summation of excitatory processes of different origin, and on the other their mutual control or modification, are what one would expect to occur on the analogy of the properties of grey matter as exhibited in reflex action. In the present communication an attempt will be made to collect from scattered sources the evidence regarding such interaction, to discuss the bearing upon sensory phenomena of concepts derived from the study of reflex action, and to emphasize the value of these concepts as working hypotheses on which future researches on the physiology of sense-organs may profitably be based.

Before proceeding further, it is worth while to remind ourselves that the integration of sense-impressions derived from two or more end-organs may sometimes be brought about in a manner notably different from that observed in reflex action. Sherrington has stressed this point in the last chapter of his book [58], where he summarizes the results of his experiments with the binocular flicker lantern [57]. These, far from showing any considerable degree of physiological interaction between the processes initiated at each retina, revealed a somewhat surprising degree of independence between the central apparatuses connected with the two eyes. So far, at any rate, as the qualities brightness and flicker were concerned, the retino-cerebral apparatus belonging to each eye was shown to develop its own sensual image with hardly a trace of interference from processes simultaneously occurring in the retino-cerebral apparatus of the other eye. The fusion of the two uniocular percepts, which had each been elaborated independently by their respective neuro-psychical mechanisms, to form a single binocular percept, appeared to be a psychological process, with no physiological basis of interaction between their respective paths below the level to which consciousness was adjunct. "During binocular regard of an objective image each uniocular mechanism developes *independently*—at least as to steadiness of brightness and intensity of brightness—a sensual image of considerable completeness. The singleness of the binocular perception results from the combining of these elaborated uniocular sensations: it is the product therefore of a psychical synthesis that works with already elaborated sensations contemporaneously proceeding" [57, p. 60]. "It is much as though, of the left and right lantern images, each were seen by one of two observers, with similar vision, and as though the minds of the two observers were combined to a single mind" (*ibid.*, p. 56).

Sherrington's experiments provided strong experimental support for the rather similar conclusions which Helmholtz [37, p. 407] had drawn from the facts of binocular rivalry, and which McDougall had based on his own experiments on the revival of faded after-images [46, pp. 217-220]. Dawson's work [22] on binocular colour mixture and observations by Tschermak [61], Snellen, and van Heuven [41] on the relation between "corresponding points" of the two retinæ have supplied additional evidence pointing in the same direction. Fechner's well-known "paradoxical experiment" [28, pp. 416-463] also receives a simpler and more plausible explanation on these lines than on any of the others which have been suggested (e.g., by Fechner himself (*loc. cit.*) or by Allen [6, 8]).

It should be mentioned, however, that De Silva and Bartley [25] have recently published a paper in which they throw doubt on Sherrington's interpretation of experiments involving comparison of uniocular and binocular brightness. They give some interesting curves showing the relative subjective brightness of a binocular field obtained by fusing two unequally bright uniocular fields, as compared with that of the binocular product of two fields, each of the same objective brightness as the brighter of the two preceding.

But I find it impossible to follow the process of reasoning by which they regard their results as contradictory of Sherrington, whom they have apparently failed to understand. They state that "contrary to the conclusions of Sherrington, we maintain that the two eyes do function integratively as regards brightness, although we concur with him that increments and decrements of intensity cannot be perfectly correlated with increments and decrements of brightness." It is difficult to know exactly what "integratively" is intended to signify in this quotation, for in its usually accepted sense, implying the combining of parts into a whole, no one who has experienced normal vision with two eyes can doubt that they so function. But if, as seems probable, they use "integratively" as synonymous with "additively," their findings hardly justify their conclusions, and seem entirely compatible with Sherrington's statement that the value of a binocular brightness "is somewhat, but not far, above the arithmetic mean of the values of the two uniocular components as expressed by the measures of the physical stimuli yielding them" [57, p. 50]. They find, for instance, that if a uniocularly seen field is taken as standard, no apparent alteration in brightness occurs when the corresponding area of the opposite retina is then exposed to a field 0·7 to 0·8 times as luminous. And Sherrington's much more important flicker experiments seem quite inexplicable except on the hypothesis outlined above.

The purpose of this digression, however, is not so much to defend Sherrington as to indicate that sensual integrations may, and almost certainly do, occur *in consciousness*, and work with already elaborated sensations or percepts. The study of such phenomena is obviously a matter for the experimental psychologist rather than for the physiologist; it is therefore not included in the present enquiry. Physiologists are concerned with the interplay of excitatory and inhibitory material processes in the synapses and cells of the nervous system, and not with interaction between sense presentations. But interaction between nervous processes in the various ascending paths of the nervous system obviously differs from this psychical interaction and is a strictly physiological problem. From time immemorial a parallelism has been recognized between the responses of consciousness and of muscles to peripheral stimulation—as witness the many proverbs about worms turning. It is, therefore, both interesting and instructive to compare the sensations evoked by appropriate stimuli with the mechanical responses or movements of an unconscious animal in purely reflex action. After-discharge, for example, is equally characteristic of both.

In this article, then, there will be considered any interaction at a sub-perceptual or physiological level between processes occurring in the nervous system as a result of stimulation of peripheral receptors, whereby alterations are produced in the sensations to which such stimulation gives rise. The interaction may take various forms, such as inhibition (the activity of one set of neurones inhibiting the simultaneous activity of another set), temporal summation, areal summation, and occlusion, but in many cases it is impossible in the existing state of knowledge to specify what the exact nature and site of the interaction may be.

Since the eye has, for many reasons, been found the most convenient sense-organ for investigation, most of the following pages will be devoted to an examination of experiments on vision. Section I deals with the retina and its central connexions; Section II with the binocular mechanism and the physiological or apsychical relations between the two retino-cerebral apparatuses. In Section III reference will be made to some cognate observations on other forms of sensation.

SECTION I.—UNIOCULAR VISION.

In view of its development as an outgrowth of the brain in the embryo, and in view of the complexity of its structure, which histological investigation [16] has revealed in the form of an elaborate system of cells and synapses, it would be surprising if the retina did not possess, in some degree, properties of interaction and coördination between its constituent elements, such as we are accustomed to find in the grey matter of the central nervous system. In a few cases, it has been found possible to prove by experiment that this expectation is well founded. But since most investigations in physiological optics have of necessity to be carried out on man, it is often impossible to demonstrate conclusively whether the site of any observed interaction is in the retina or in the paths connecting the retina with the sensorium.

The human retina, indeed, offers advantages in some respects, as compared with the central nervous system of the decerebrate or decapitate animal, in the investigation of problems of convergence. Its temperature, nutrition, and oxygen supply are less liable to accidental fluctuation during an experiment; it is easier to grade stimuli both as to intensity and as to extensity; and the pitfalls incidental to the use of mixed afferent nerves in the reflex preparation do not beset the worker who applies only normal adequate stimuli to his own rods and cones.

There are at least four distinct ways in which physiological integration of processes originating at neighbouring retinal areas may be brought about. First, impulses from many rods and cones in the peripheral parts of the retina may impinge upon a single bipolar cell, and many bipolar cells transmit impulses to one ganglion cell. Chievitz [18] found 80 rods and cones connected with a single ganglion cell at a point 6 mm. from the fovea centralis of a human eye. Secondly, there are cells in the retina with branching processes forming synapses with a number of bipolar or ganglion cells [16, pp. 364-365]. Thirdly, transverse connexions between the central paths in the lateral geniculate bodies, thalamus, and occipital cortex may co-ordinate the transmission of impulses through these centres. Lastly, the existence of efferent fibres running from the brain to the retina by the optic tracts and optic nerves is well established [16, pp. 366-367].

Classification on these anatomical lines being out of the question, it will be found convenient to group our examples by the character of the interaction which is manifested. Where possible, the site at which the interaction occurs will incidentally be referred to.

A.—Temporal Summation.

That the intensity of the resulting sensation is to some extent dependent on the duration of the light stimulus has been known since the time of Plateau. Quantitative investigation has concerned itself principally with the threshold intensity of stimuli of varying brief duration. Charpentier [17], in particular, established that feeble lights, which are invisible when they act for less than 125 σ, may be made visible by mere prolongation of their time of action. Summaries of the conclusions of other workers in this field will be found in Parsons [51, pp. 94-99], and Lythgoe [45, p. 38]. Experiments on the excised eye of the conger eel [Adrian and Matthews, 4] have shown that the interval between the beginning of a flash of light and the discharge of impulses along the optic nerve varies inversely with the duration of the flash.

A large proportion of this summation may reasonably be ascribed to the accumulation of products of photo-chemical reactions in the rod and cone layer of the retina, rather than to any process of facilitation at synapses. But since there is much reason for believing that the excitatory process at synapses in the nervous system also represents some cumulative alteration in physical or chemical conditions [59 ; 27 ; 2, pp. 145-146], it would be academic hair-splitting to attempt a rigid differentiation between these two mechanisms. In the same way that prolonged after-discharge is specially characteristic of reflexes exhibiting temporal summation or recruitment [44], so visual sensation long outlasts stimuli of brief duration.

B.—Spatial Summation.

For over fifty years (see Parsons [51, pp. 130-137]) it has been known that in the fovea centralis the threshold luminosity of a stimulus varies inversely with the area of that stimulus (Riccò's Law). In other words, the threshold is determined by the total quantity of light falling on the fovea in unit time. On the other hand, in the periphery of the retina, where anatomical structure would seem to indicate greater opportunity for spatial summation, no such simple relationship between extensity and intensity has been found to exist. According to Piper [54; see Parsons, *loc. cit.*], the stimulation value of a luminous surface for the dark-adapted periphery is proportional to the square root of the area of the retinal image. The law is stated to be valid only for mixed white light, only for objects subtending between 1° and 10°, and only for the dark-adapted eye.

In recent years, methods other than that of threshold determination have been employed in the attempt to elucidate the question, and have served both to confirm these earlier conclusions and to amplify them. In an important series of papers, Adrian and Matthews [3, 4, 5] have proved that spatial summation occurs as a purely retinal process in the excised eye of the conger eel. Recording action-currents in the optic nerve on stimulating the retina with light, they first showed [3] that when the retinal image does not exceed 1 mm. in diameter the effects of an increase in the size of the image are the same as those of an increased intensity of illumination. The maximum frequency of the discharge, and the latent period preceding the occurrence of electrical changes in the nerve, were both found to be determined approximately by the product area x intensity.

In later experiments with the same preparation [5] they found that when the entire retina of the conger eel is exposed to uniform illumination, the action-current discharge in the optic nerve may lose its usual irregular character after 5-10 seconds and may consist of a series of regular waves with a frequency which commonly varies between 15 and 5 a second. These "waves . . . are caused by a rhythmical waxing and waning in the number of impulses in the nerve fibres. It follows that the ganglion cells of the retina must all be working in unison with alternating periods of rest and activity. . . . We conclude that the rhythmic discharges from the retina are due to nervous interconnection between the ganglion cells." Strong support for this conclusion was afforded by the fact that strychnine favoured the occurrence of the rhythmic discharge.

Further evidence of interaction between retinal neurones was obtained by illuminating four small areas of the retina. "When four points . . . [separated by 30° visual angle] are illuminated simultaneously, the reaction time of the optic nerve discharge is shorter than when any one of the points is illuminated alone. Strychnine causes a marked increase in the range over which this interaction can occur, and we conclude that it is due to a nervous summation in the synaptic layers of the retina." The view that the interaction here is a process of nervous summation is also indicated by Granit's demonstration [38] of a similar phenomenon in the human retina, as evidenced by flicker observations. Using four circular images, each subtending 1° of visual angle and with a space of 0·4° of visual angle separating each from its neighbours, he has compared the critical frequency for extinction of flicker when all four are illuminated with that when only one patch is bright. In five observers he found the former value invariably higher than the latter when a point 10° from the centre of the "constellation" was fixated. With an illumination of 94·7 metre-candles, figures actually obtained varied from 29·19 and 26·06, to 20·95 and 18·64 respectively. The same effect was observable with an illumination of 0·947 m.c., and was still present when the patches were 1·4° apart. With central fixation, only the merest trace of interaction could be detected. This is precisely what might be anticipated from the differences in structure between the centre and the periphery of the retina.

A puzzling feature of the findings of Adrian and Matthews [5] is that, for any given constellation, the reaction time is longer after than before strychnine. It is difficult to attribute this to a depressant action of the drug on the receptor elements, since strychnine enhances the power of light perception in man [42]. It may perhaps indicate the occurrence of some interaction of a quite different nature from simple summation.

Granit and Harper [34] have also made detailed observations on the influence of area (A) of stimulus on critical frequency (n) for extinction of flicker at a number of different intensities (I) of stimulus. These show that, both in the centre of the field of vision and 10° from the fixation point, the following relation between n and A holds for objects subtending between 6° and 21° of visual angle: $n = c \log A + d$, where c and d are constants. The value of c is higher in the periphery than in the centre. The relationship is clearly suggestive of the well-known Ferry-Porter Law relating n and I; an increase in area, in fact, is exerting the same sort of influence as an increase in intensity *cf.* Exner [27A]).

An even more striking result of these experiments is that, for a given value of n, the product $I \times A$ is found to be constant in the peripheral parts of the retina over a wide range of values of I and A. This is not true of the centre, and is a further illustration of the great summative powers of the periphery. For very high values of I, an increase in A does not result in a corresponding decrease in I. This may readily be interpreted as a phenomenon allied to "occlusion" [19]. Kleitman and Piéron [43] have also produced evidence that the peripheral parts of the retina possess much greater powers of areal summation than does the fovea. The physiological consequences of convergence of many nerve paths on a common path are thus well exemplified in the eye.

When more work along these lines has been accomplished, it may be possible to specify the conditions under which each of the three recognized types of effect of convergence, viz., occlusion, algebraical summation, and overlap of subliminal excitation in ganglion cells or elsewhere [see 24], is likely to occur. The results of Piper and others on the relation between area of stimulus and threshold intensity will then be easier to interpret.

C.—Simultaneous Contrast Phenomena.

Helmholtz, among others, has denied that there is any physiological basis for simultaneous contrast. "Pure simultaneous contrast," he says [38, p. 252], "is dependent on an alteration, not of sensation, but of judgement." Psychological factors undoubtedly play a part, and in some experiments (e.g., that described by Waller [62]) a large part, in the phenomenon. But many independent proofs have been adduced which demonstrate an apsychical or low-level interaction as an important element.

One of the most convincing confutations of Helmholtz' view is the well known experiment of Hering [40], which is sometimes erroneously attributed to Burch who merely elaborated it [15]. In it a red field is viewed with one eye and a blue field with the other. When these two fields are binocularly combined, they appear as a homogeneous purple. On each field is placed a grey cross. The cross which is surrounded by the red field appears green, and that surrounded by the blue field appears yellow, although introspection is unable to analyse the combined background into its two components. The apparent colours of the two crosses are therefore induced in them before the binocular colour fusion has occurred and cannot be attributed to an error of judgement. Conscious judgement could only contrast the crosses with the homogeneous field and *both* should appear in the colour complementary to purple, viz. yellow-green. Hering concludes that colour contrast is not dependent on psychological factors but on the "physiological processes set up by the external light in each single half of the organ of vision (in the widest sense of this term)."

Sherrington [56] has also devised a number of ingenious experiments to demonstrate "a reciprocal physiological relation between units of the retino-cerebral apparatus such that activity of the apparatus connected with a point of retinal surface P affects the reactions of the apparatus belonging to the retinal area circumjacent about P." The experiments are performed with rotating discs. The neatest is perhaps one in which the disc is divided by a diameter into a black half and a yellow half. On this background are two narrow rings, each of which is half black and half light blue. In one ring the black is surrounded by black and the blue by yellow, while in the other the relations between ring and background are reversed. On rotating the disc, flicker is found to cease in the first ring at a speed (e.g., 22 revs. per sec.) at which it is still well marked in the second (requiring 34 revs. per sec. for extinction of flicker). The background at both these speeds is so completely confused, if not fused, that it cannot be decided by introspection that there is any difference between the relations of the ring segments to their backgrounds. Moreover, at speeds insufficient completely to abolish flicker in the rings, the first ring appears definitely darker than the second. The blue segment on the yellow ground is evidently being darkened, and the blue segment on the black ground is being brightened, by simultaneous contrast. And this areal induction is obviously occurring at a sub-perceptual level and cannot be attributed to conscious judgement, since no introspective analysis of the objective data is possible.

F. Allen's researches on "visual sensory reflexes" are chiefly important for their bearing on the problems of colour vision. But they also represent a notable contribution to the subject of this article. By measuring the critical frequency for extinction of flicker in small patches of monochromatic spectral light under various conditions, he has shown for example [7] that stimulation of one area of retina induces alterations in the apparent luminosity of certain parts of the spectrum as seen with other regions of the same retina. With the exception of six "equilibrium colours," a patch of monochromatic colour of any wave-length between 740 $\mu\mu$ and 410 $\mu\mu$ causes enhancement of the red, green, and violet colours when the latter are examined by the flicker method in neighbouring parts of the retina. The predominant enhancement is in the portion of the spectrum complementary to the "active" colour. When white light and darkness are used as stimuli instead of colours, enhancement of the whole spectrum results. Under certain conditions [8] "reflex depression of sensitiveness" has also been demonstrated.

The connexion between these experiments and the phenomenon of simultaneous contrast is sufficiently clear to make further comment unnecessary. Whether the mechanism responsible for Allen's effects is situated in the retina or in the brain remains to be proved.

Successive contrast may be explicable—in part at least—in a similar way. For Allen finds that after monochromatic stimulation of an area of retina, the sensitivity of that area is depressed for light of the same wave-length as the fatiguing colour, but enhanced for that of other colours. There are obvious analogies between successive contrast and reflex rebound, but since neither phenomenon is at all fully understood, it would be unwise to press the analogy far.

D.—Inhibition in the Retino-Cerebral Apparatus.

G. E. Müller [47] has described, under the term "Liebermannsche Hemmung," the occurrence of an inhibition of the cone mechanism by the rod mechanism. The idea was suggested to him by Paul von Liebermann in explanation of certain features of the central scotoma in twilight vision. The researches of himself and his associates on the sensation-time of narrow feeble stimuli moving across the field of vision provided definite evidence in its favour.

Granit [31, 32] has made extensive investigations on the duration of so-called "after-images of movement" following stimulation of different areas of retina. He was led to the conclusion that the unexpectedly short duration of the after-effect under certain conditions in which both rods and cones have been excited must be attributed to inhibition of the latter mechanism by the former. Grindley [35] has recently criticized this interpretation because he could find no evidence of such an influence in experiments carried out by a different method. His argument is based on the doubtful assumption "that red light of wave-length greater than about 6,700 A.U. stimulates only the cones of the retina" and not the rods.

Evidence of another kind is forthcoming from experiments by Creed and Granit published in 1928 [20]. The aim of the research was to study the factors influencing the latent period preceding the development of ordinary negative after-images. Only such observations as have a direct bearing on the present argument will be referred to here.

The experiments were carried out in a photographic dark-room lighted by a single opal-glass electric lamp at one end of the room. Against the evenly black wall at the opposite end of the room, white circular discs, provided with a fixation point, were observed binocularly. At the end of the fixation period (fifteen seconds) the experimenter lowered a screen (of the same white as the object) over a pulley, thereby covering the disc. The observer rapidly directed his gaze on to a fixation mark placed in the middle of the screen and so arranged as to be directly over the mark previously fixated on the disc. As soon as he saw the negative after-image appear, he said "On," and the experimenter, who was provided with a stop-watch, noted the time. For the next observation, experimenter and observer changed places.

When experiments were made with discs of varying size in the centre of the field of vision, it was found that the latency progressively shortened as the visual angle subtended by the disc was increased from about 40′ to about 4°40′. Discs subtending 5° or 6°, however, showed a renewed lengthening of the latency, often amounting to more than 1 second. On further increase in the size of the disc, the latency again shortened. The most interesting feature of the experiment was the fact that the after-images of discs subtending 5° or 6°, discs the edges of whose images were falling on a region where rods were replacing cones as the predominant receptor cells, showed a longer latency than did those of larger and of smaller discs. This gave a "hump" or secondary rise on a graph in which latency was plotted against visual angle.

A disc of 14 cm. diameter, viewed from a distance of 1·50 metres, occupies this position on the curve in most observers. Its edge falls in what may be termed the transitional area, where the latent period is longer than that in areas more central and more peripheral. One might anticipate, therefore, that the after-image would first appear as a ring of about 12 cm. diameter and then, either gradually, or perhaps at once, spread inwards and outwards until the disc was complete. In practice nothing of the kind occurs. There is no sign of a negative after-image at the end of the latent period characteristic of a 12-cm. disc. Not until 1 second or so later does the after-image appear, and it is seen from the first as a complete dark disc. The edge seems to be the determining factor, and the after-effects in consciousness of previous stimulation of areas of retina within that edge seem to be inhibited for about 1 second. The finding sheds some light on the means employed to overcome the difficulty of possessing in the retina two structures (rods and cones) of different sensitivity and functions, and to combine them in use as a single sensory organ. For if we are right in interpreting the hump as due to the excitation of rods, we have here in the transitional area the rod mechanism coming into action in overwhelming force and actively inhibiting the after-effects which would otherwise have followed stimulation of cones.

When similar experiments were made with the centre of each disc 11 cm. (4° 12′) to one side of the fixation point, the results were entirely different. The latent periods for discs of all sizes were found to be exactly the same. In these experiments the images of discs of 20 cm. and more in diameter must have fallen partly on the fovea, and when the diameter was more than 22 cm. they overlapped the fixation point. The facts that the latency was not then lengthened and that the after-image was seen as a complete whole from the moment of its first appearance, afford further evidence of the rods being the controlling power when a large number of rods and a small number of cones are stimulated together. If the conditions were reversed, it might perhaps be possible to obtain evidence of an extensive stimulation of cones inhibiting the after-effects of a restricted stimulation of rods, but we have no evidence on this point.

The experiments just described supply indubitable evidence of interaction, but it should be pointed out that the nature of that interaction may conceivably be summation and not inhibition. If Ebbecke's view [26] be correct, viz., that negative after-images indicate a central reaction antagonistic to retinal after-stimulation, it would seem that the longer latencies in our experiments indicate a longer duration of the retinal excitation which precedes the swing-back of the pendulum. (In this event, the short latencies with discs subtending 4° must mean an inhibition affecting the most central areas.) According to other theories, such as McDougall's [46, p. 77], there is no essential difference between the mode of causation of positive and negative after-images. There is thus every reason for adopting the traditional cautious attitude of physiologists in drawing precise conclusions from observations of after-images.

SECTION II.—PHYSIOLOGICAL INTERACTION BETWEEN THE TWO RETINO-CEREBRAL APPARATUSES.

It has been pointed out already that the integration of sense impressions derived from corresponding areas of the two retinæ is not necessarily a physiological process at all, but may be a psychical synthesis of previously elaborated uniocular percepts. Many of the older writers, though not all, attempted to explain the binocular sensory mechanism entirely in terms of physiological interaction or innate antagonism between nervous processes initiated at the two retinæ. Thus, Fechner summarized his conclusions on binocular brightness and colour mixture by saying "zwischen beiden Netzhäuten besteht ein antagonistisches Verhältniss" [28, p. 559]. Hering's [39] law of "complemental shares," according to which rivalry is really occurring even with similar right and left uniocular images, may be regarded as a further development of Fechner's theory. Panum [50, p. 89], in his classical work on the prevalence of contours in binocular rivalry, followed Roger Bacon [14A], Newton [49], and Johannes Müller [48] in imagining that the impulses from corresponding points in the two retinæ converge to a single common centre or point of the sensorium, and that this convergence of the conducting paths explains the singleness of the binocular percept. For an able account of the views of early writers, the reader is referred to Aubert [14, p. 305 *et seq.*].

None of these lines of reasoning commended themselves to Helmholtz, who [37, p. 407] found it impossible to explain the influence of attention on binocular rivalry without assuming that "the content of each separate field reaches consciousness without being fused with that of the other field by means of organic mechanisms, and, accordingly, that the fusion of the two fields in one common image, when it does occur, is a psychical act."

Sherrington's experiments leave no room for doubt that binocular fusion is essentially a psychical phenomenon and is not due to any low-level confluence of the twin paths from the retinæ. "The cerebral seats of right-eye and left-eye visual images are shown to be separate. Conductive paths no doubt interconnect them, but are shown to be unnecessary for visual unification of the two images" [58, p. 383].

We now pass on to consider what evidence there is for the existence of such connecting paths, and what functions can be assigned to them. For they only can be concerned in the interactions which we are discussing. Binocular colour mixture and brightness fusion must be excluded from the argument, since we have no direct means of knowing to what extent the synthesis in these cases is a combination of sensations existing contemporaneously in consciousness, and to what extent it is a sub-perceptual or physiological process.

Interaction at a physiological level was evidenced to a small degree in some of Sherrington's flicker observations. When, for instance, alternations of light and darkness in the two uniocular images were arranged to be in opposite phase, flicker was found to be abolished at a very slightly lower critical frequency (e.g., 95·8 per sec.) than when the flickerings were exactly in phase (97·3 per sec.). "From these observations it appears that similar phases of flickering illumination if timed to fall coincidently on conjugate retinal areas do *very slightly reinforce* each other in sensation, and if timed exactly alternately do very *slightly mutually reduce.* But the *broad outcome of the observations is that* so far from bright phases at one eye effacing dark phases at the corresponding spot of the other eye, *there is hardly a trace of any such interference.* To judge from its absence of influence on the flicker rate, the dark phase incident at retinal point A does not, as regards sensual result, modify the bright phase synchronously incident at the conjugate retinal point A′, and conversely. If the brightness of the bright phase or the darkness of the dark phase were lessened at A by A′, the rate of frequency of stimulus for extinction of flicker must fall. But except in minute and perhaps equivocal degree it does not alter" [58, p. 365]. Here then is slight, but almost negligible, evidence for some degree of convergence or interaction between the two retino-cerebral paths.

No further clear evidence of physiological interaction appears to have been forthcoming until 1923, when Allen [6] fatigued one eye with monochromatic spectral lights. He then found, by measurements of the critical frequency for extinction of flicker, that the brightness of certain parts of the spectrum (in the red, green, and violet) was enhanced for the other eye by some "reflex process." The effects were similar to those described above as occurring in other areas of the same retina, and the same six "equilibrium colours" were devoid of effect. He also found that the effect of darkness adaptation of one eye upon the other was to cause a diminution of brightness of the whole spectrum. Gellhorn [30] has also described alterations in the excitability of one eye following stimulation of the other.

Allen suggests that the sensitivity of the rods and cones of the second eye may be reflexly increased by impulses reaching them by nerve-fibres running directly from one optic nerve to descend in the other. There appears, however, to be no good evidence for the existence of such a nervous commissure between the two retinæ [16, p. 375]. The site of the interaction must, therefore, be central—in the thalamus, lateral geniculate body, or cortex. It seems unnecessary to postulate any change in the *receptors* of the second eye, but if their excitability be affected, the efferent pathway may well be the fibres which pass outwards to the retina in the optic tracts and optic nerves. It is at least equally probable that the whole effect is central, and that some influence on the transmission of excitatory processes through the grey matter of the central nervous system is exerted by the contralateral retino-cerebral apparatus.

Other experiments demonstrating interaction between the two uniocular mechanisms have been published by Creed and Harding [21]. The principal object of the investigation was to determine how the time-relations of the negative after-image of a simple white object, seen uniocularly, might be modified by projecting the after-image on to a screen presented to the other eye. The technique adopted was much the same as that of Creed and Granit, and need not again be described in detail.

In preliminary experiments it was found that the latent periods preceding uniocular after-images projected into complete darkness are much longer than those preceding binocular images similarly projected. The uniocular mechanisms, therefore, reinforce one another at a subconscious level; for by no purely psychical combination of independently elaborated uniocular percepts could a binocularly aroused after-image become visible at a time when nothing but a homogeneous dark field would be seen with either eye acting alone.

In a series of fifteen experiments it was observed that when a uniocular black-projection after-image is in rivalry with a white field presented to the other eye, it appears earlier than when, in the absence of any stimulus to the other retina, it might be expected to develop with less hindrance. The conclusion seems inescapable that somewhere an interaction is occurring between the retino-cerebral apparatuses of the two eyes, and that the formation of an image of a plain white screen on one retina is facilitating the early development of an after-image of a white object previously presented to the other eye; for, at the time when the after-image is first seen, nothing but a uniformly dark field would be visible with the latter eye acting alone, and nothing but the white screen with the former eye acting alone. A psychical fusion or rivalry of a rectangular white screen with a uniform dark field could not produce a negative after-image of a circular disc.

We can hazard no guess as to the site or nature of the interaction in these cases. The mode of production of after-images is still so uncertain that it is impossible to say whether inhibition or summation or some more complicated process should be invoked to account for the results. It should be emphasized, however, that the validity of this argument for interaction is not bound up with any particular theory of the seat and mode of causation of after-images. There is no alternative to interaction between the retino-cerebral apparatuses of the two eyes, at a sub-perceptual level in the brain, as the explanation of the results.

To summarize, it is clear that binocular fusion and rivalry, whether of contours, of brightness, or of colour, are mainly psychical phenomena involving interplay between sensations and percepts. There is no appreciable convergence of the conducting paths from corresponding areas of the two retinæ to form a final common path to the sensorium, and low-level connexions between the two paths are not required to accomplish the synthesis of sense impressions derived from the two eyes. Some of Sherrington's experiments, however, revealed a trace of interaction such as would be produced by a slight degree of "convergence."

Allen demonstrated the effects of stimulation and darkness adaptation of one eye upon the luminosity of a spectrum seen with the other eye. These effects must play some part in such phenomena as Fechner's paradoxical experiment and binocular contrast, though possibly their discoverer tends to over-estimate their importance in these connexions. Creed and Harding have supplied further proof of interaction between the two retino-cerebral apparatuses as evidenced by effects on the time-relations of negative after-images. There can therefore be no doubt about the existence of functional inter-connexions, such as Fechner, Hering, and others had unjustifiably assumed to regulate normal vision. Further work is required to elucidate their precise rôle in binocular vision.

SECTION III.—EXAMPLES DRAWN FROM SENSES OTHER THAN VISION.

Henry Head has provided us with many excellent examples of physiological interaction between simultaneously occurring excitatory processes in the various sensory tracts of the spinal cord and brain, whereby the arrival at the sensorium of impulses subserving certain forms of sensation (especially cold and pain) is inhibited. For a full account of his experiments, observations, and inferences, his collected works [36] should be consulted. Only a very brief summary of some of his more outstanding contributions to the subject under discussion will here be attempted.

There seems little room for doubt about the interpretation of his experiments on the sensitivity to hot water of the glans penis (1908; *loc. cit.*, pp. 275 and 325). In some individuals the tip of this organ is quite insensitive to heat, though well endowed with endings responding to painful stimuli and to cold. There appear to be no heat spots except in the neighbourhood of the corona. Vessels containing water at various temperatures were raised until the surface of the water covered the glans but did not touch the foreskin. Contact with the fluid was not appreciated; if, therefore, the temperature of the water was such that it did not produce a sensation of heat or cold, the subject was unaware that anything had been done. Thus, with water between 26° C. and 38° C., no sensation of any kind was produced until the foreskin was reached. Water at 38° C. over the tip and body of the glans produced slight aching; at 40° C., unusually disagreeable pain; at about 43° C., it became extremely painful. When the water was raised to 45° C., the pain was to a great extent displaced by a vivid sensation of cold ("paradoxical cold stimulation"). But, as soon as the water covered the corona without reaching the foreskin, both cold and pain disappeared, giving place to an exquisitely pleasant sensation of heat. The impulses, which must have been evoked from the end-organs for pain and for cold by contact with the water at 45° C., were inhibited by those consequent on stimulation of the heat spots.

It is difficult to attribute this inhibition of pain by cold, and of pain and cold by heat, to a psychical interaction between sensations or percepts. It is a matter of universal experience that the immediacy and urgency of pain are such that it tends to monopolize the whole attention of an individual. Only under conditions of quite exceptional excitement (and, perhaps, also of long and careful training, as in Pavlov's conditioned reflexes in response to stimuli which normally evoke pain [52, pp. 29-30]), can pain be driven out of consciousness by other psychological events and processes. Normally, pain of any considerable severity absorbs the whole mind and renders the perception of other sense impressions indistinct and difficult. It seems fairly certain, therefore, that the pain impulses in Head's observations never reached the level at which consciousness is affected. The passage of impulses in the pain tracts was inhibited at an apsychical level by excitatory processes occurring simultaneously as a result of the stimulation of heat and cold receptors.

Head finds reason to believe that a similar integrative mechanism is normally at work in regulating the passage of all sensory impulses from the skin and deep tissues to the sensorium. The phenomena of intensification and peripheral reference, which are marked features of pain impressions at a certain stage in the recovery of cutaneous sensibility after division of a peripheral nerve, are believed by him to be due to the early restoration of function of a primitive protective sensory mechanism which he calls protopathic. Only later does the discriminative or epicritic system (subserving light touch in hairless areas and certain aspects of temperature sensibility) resume its activity. The latter system controls, and to a large extent inhibits, the impulsive activity of the former, which alone is present in the skin covering the glans penis. The strange sensory responses which are elicitable from such areas are due to release of protopathic function from the control normally exercised by the epicritic system.

Similar conclusions about the inhibition of pain have been reached by Foerster [29] as a result of a vast clinical experience of injury and disease of the nervous system. He states, for example: "Der inhibitorische Einfluss der Empfindungssysteme auf die Erregbarkeit

des Schmerzsystems muss nun aber ausser an den Hinterhornsegmenten auch noch an anderen Stellen des Schmerzsystems angreifen. Wir beobachten nämlich Spontanschmerz, Schmerzirradiation und Hyperpathie auch bei Unterbrechung der langen aufsteigenden Hinterstrangbahnen. Bei einer Durchtrennung der letzteren in der Höhe des sechsten Dorsalsegmentes kommt es z.B. zu einer Hyperpathie aller infraläsionellen Dermatome D7-S5" (*loc. cit.*, p. 164).

The determination of the anatomical site of this interaction presents some difficulties. It may be due in part to the passage of inhibitory descending impulses from the cerebral cortex to lower parts of the central nervous system, and in part to transverse communications between the afferent tracts on their way towards the thalamus and cortex. That important cortico-thalamic inhibitory paths exist seems clear from the clinical study of lesions involving the optic thalamus and isolating it to a greater or less extent from the cerebral cortex. The so-called "thalamic syndrome," first described by Dejerine [23] and Roussy [55], and since studied in detail by Head, Foerster and others, has as one of its salient characteristics acute pains in the half of the body opposite to the lesion. The pain is commonly spontaneous, persistent, paroxysmal, often intolerable, and yields to no analgesic treatment. "The lateral part of the optic thalamus is the organ through which the cortex can influence the essential thalamic centre, controlling and checking its activity. The excessive response to affective stimuli, so prominent a feature of lesions in this situation, is not due to irritation but to removal of cortical control" (Head and Holmes, 1911; *Op. cit.*, p. 597). Stopford [60] has argued that the first of the two stages in recovery after division and suture of peripheral nerves is due to the thalamic sensory mechanism coming into play before the cortex has had time to readjust itself to new conditions.

Foerster postulates a whole series of inhibitory paths descending from the sensory cortex to all levels of the nervous system. "Wir haben von den Hemmungsmechanismen, welche auf das Schmerzsystem einwirken, bisher nur des afferenten perzeptorisch-epikritischen Systems gedacht. Ich habe aber in den vorangehenden Kapiteln bereits mehrfach darauf hingewiesen, dass wir Grund haben, anzunehmen, dass es eine corticofugale, also efferente Schmerzhemmungsbahn gibt, die vom Cortex cerebri zu den einzelnen Stationen des Schmerzsystems, zum Thalamus opticus, zum Grau der Formatio reticularis and zu den spinalen Hinterhornsegmenten abwärts zieht" (*loc. cit.*, p. 166). He even implies that the peripheral receptors themselves are normally subject to inhibition: "Normaliter . . . diese Einwirkungen . . . sind unterschwellige Reize für die Schmerzrezeptoren. Wenn aber durch den Ausfall der Empfindungssysteme die Erregbarkeit des Schmerzsystems beträchtlich erhöht wird, so bilden diese Einwirkungen für die Schmerzrezeptoren nunmehr einen überschwelligen Reiz, und es kommt zum Schmerz" (p. 162).

But I can find no proof of the occurrence of such descending paths below the level of the thalamus. The facts can be equally well explained by interaction between the ascending processes in the spinal cord, brain stem, and thalamus. The thalamus is undoubtedly a highly important factor in the integration of sensory processes of all kinds, and is probably the principal site of the interactions we have been considering. Its importance is well expressed by Foerster in the following sentences (p. 166). "Ich habe darauf hingewiesen, dass der Thalamus opticus nicht nur als funktionelle Einheit für das Schmerzsystem der kontralateralen Körperhälfte bzw. beider Körperhälften aufzufassen ist, sondern auch für alle afferenten Systeme des Organismus überhaupt, für alle sensiblen und sensorischen Systeme. Das kommt dadurch zum Ausdruck, dass bei Herden, welche die Schleife unterbrechen, Spontanschmerzen durch einen an sich ganz geringfügigen nicht schmerzhaften sensiblen Reiz, der irgendwo am Körper angreift, aber ebenso auch durch irgendeinen Sinnesreiz, einen optischen, acustischen, olfactorischen oder Geschmackreiz ausgelost oder gesteigert werden kann."

We are on less certain ground when we attempt to find evidence of interaction taking forms other than inhibition. But at least two examples of summation may be given.

Spatial summation is exemplified in the familiar effect of area on the intensity of the sensation evoked by a thermal stimulus [63].

"Immediate induction" is shown by the great potency as a skin stimulant of a moving object. The effect in consciousness is exactly parallel to the reflex effect in the spinal animal, which Sherrington has graphically described thus. "A subliminal stimulus applied at a point A will render a subliminal stimulus applied at a point B near A supraliminal if the second stimulus follow within a short time, e.g., 500 σ. The space of receptive surface across which this can be demonstrated in the scratch-reflex amounts to 5 to 6 cm. It is best worked out by unipolar application of the induced current through a stigmatic electrode—fine gilt entomological pin. In that way numerical values can be assigned to the results. But the phenomenon is characteristically and simply illustrated by the difference between the potency as a stimulus of the edge of a card, say 6 in. long, pressed simultaneously its whole length against the receptive skin-field, say for five seconds, and on the other hand lightly drawing one corner of the card along the same line in the skin-field also for five seconds. The former application simply evokes a reflex of a few beats, which then dies out. The latter evokes a vigorous reflex that continues and outlasts the application of the stimulus. A successive line is more effective as stimulus than a simultaneous line of equal length and duration. . . . The same thing is seen with a spur wheel. Even when the points are two centimeters apart, as the spur wheel is rolled over the surface successive summation occurs, and the reflex is evoked as the progress of the wheel proceeds. If a parasite in its travel produces excitation which is but close below the threshold, its progress is likely to so develop the excitability of the surface whither it passes that the scalptor-reflex will be evoked. In the skin and the parasite respectively we have, no doubt, two competing adaptations at work. It is perhaps to avoid the consequences of the spatial spread of the 'bahnung' that the hop of the flea has been developed" [58, pp. 184-185].

Finally, there remains to be considered a series of researches by Frank Allen and his associates on the critical frequency for sensory fusion of intermittent stimuli, when the latter are applied to endings of touch, taste, temperature, pain, and hearing. The experiments represent a successful application to other senses of a method which had for long been found of value by workers on vision. When a flickering light is observed, the critical frequency of intermission, such that the image just loses its flickering quality and appears as if steadily illuminated, varies with the intensity of the illumination. A mathematical formula which expresses with considerable accuracy the relation between intensity and critical frequency, as found by experiment, is the Ferry-Porter law :—

$$F \left(= \frac{1}{D}\right) = k \log I + c$$

where F = critical frequency, D = duration of each phase of light or darkness, I = intensity, and k and c are constants.

When an interrupted jet of air at known pressure is made to impinge on the skin [9, 11], it is found that the critical frequency likewise increases with the intensity of the stimulus (as measured by the pressure of the jet), and that the two can be related by the formula $D = -k \log P + c$. Actually two fusion points are found for each pressure employed, and these probably correspond to cutaneous and deep end-organs. When D is plotted on squared paper against P or against log P, two approximately parallel curves are thus obtained. When the skin area is fatigued by rubbing, both curves are shifted in such a way that a lower frequency (higher value of D) is required for each value of P. But if the area under investigation has previously been very gently stimulated by passing the tip of a feather lightly over it for about ten or fifteen seconds [11], or if neighbouring skin areas are simultaneously being stimulated [9, 11], the curves are shifted in the opposite direction. Allen interprets this as a " reflex enhancement " of the acuity of touch, comparable with the visual effects which were described in Sections I and II of this article.

When the taste organs of the tongue are intermittently stimulated with an electric current, a series of four approximately parallel curves are obtained [12], corresponding with the four primary sensations. A slightly different formula is required in this case to express the relation between the strength of stimulus and the critical frequency, viz.,

$$\frac{1}{D} = -k \log Q + c$$

where Q is the quantity of electricity passing through the tongue during each period of stimulation. The normal curves may be made to shift in either direction by appropriate means, just as was found in the case of touch; but I have some difficulty in understanding the criterion by which Allen determines whether a given shift indicates enhancement or depression. I am inclined to think that what he calls enhancement is really depression, and *vice versa*.

By a rather different technique, involving measurement of the increment of sound which, when added to the intensity of a tone previously emitted, is just perceptible, similar evidence of depression and enhancement of auditory sensitivity as a result of previous stimulation of the ipsilateral or contralateral ear has also been obtained [13].

Less easy to interpret are the abrupt changes in slope which are always found in curves expressing linear relations between intensity and critical frequency. These curves conform to the following equations:—

Vision: $\frac{1}{D} = k \log I + c$

Taste: $\frac{1}{D} = -k \log Q + c$

Hearing: $D = k \log P + c$

Touch: $D = -k \log P + c$

(The last equation also fits the values obtained on electrical stimulation of the endings of cold, pain and pressure [10]). The occurrence of a sudden change in slope, or alteration of the values of the constants k and c, at an intensity of illumination with white light of about 0 25 metre-candle, has been recognized in visual flicker experiments for the last thirty years, and has been attributed to a transition from cone vision to rod vision at low intensities [see 51, p. 104; also 53].

There seems no doubt that this explanation must now be abandoned. In the first place, Allen finds [12, 8] that each graph in vision (constructed for monochromatic light) consists of at least three, and probably five, branches, instead of the two which had previously been described by Porter, by Ives, and by himself. And in the second place, inflexions of precisely similar appearance are noteworthy features of results obtained in work on other senses, such as touch, taste, and hearing, where there is reason for believing that the receptors are a homogeneous group. "In each sensory system there is some critical intensity of stimulation at which the rate of response to interrupted stimuli, or the sensitiveness, suddenly increases or decreases" [9, p. 362].

This fundamental discovery is interpreted by Allen as follows: "First, the change may be in the receptor organs proper, which would indicate that at a definite intensity of stimulation their sensitivity becomes greater or less than before. Second, the nerve impulses may have a freer or a more hindered passage through the synaptic resistance of the reflex arc when this critical intensity is exceeded. . . . Investigations on vision . . . indicate that the first of these is correct, and also lay bare the underlying cause of the phenomenon. For when a stimulus is applied to any receptor, not only does a sensation result, but in addition two sets of reflex impulses are simultaneously generated or released and conducted from the cortical centres to the receptors, one of which causes depression (inhibition) of their sensitivity, and the other enhancement (facilitation). Through one range of intensities depression exceeds enhancement, and through another enhancement exceeds depression. The stimulus whose intensity corresponds to the point where the slope changes excites both depression and enhancement equally" [12, p. 395]. In a later paper [8] the argument is developed at greater length. It seems likely, however, that the second alternative will ultimately prove to be the right one, and that the phenomenon is in reality a central effect.

CONCLUSION.

It is abundantly clear that the afferent pathway from a receptor organ to the higher levels of the brain is not to be visualized as a telegraph line—not even as a trunk line with relays at various stages. The central nervous system acts in this connexion as much more than a complicated telephone exchange. Messages brought into it along peripheral nerve-fibres are not transmitted to the sensorium in anything like their original form. They influence, and are influenced by, other messages arriving from end-organs of similar and of diverse function. Sometimes they are inhibited or cancelled, sometimes they reinforce or facilitate one another's action. Always the message as ultimately delivered depends upon the past and present events in the transmitting system as a whole.

Adrian [1] has taught us much about the way in which excitation is conveyed from sensory endings to the central nervous system. But it would be a mistake to suppose that these peripheral events represent the physical basis of perception and sensation in the intact animal. Before the impulses reach levels in the brain at which consciousness is affected, they initiate, and are acted upon by, processes which modify to a greater or less extent the pathways by which they are ascending. Every relay, too, gives opportunity for alteration of rhythm and for after-discharge.

This physiological interaction between trains of centripetal impulses has formed the subject of our enquiry. It needs, in the present state of knowledge, to be carefully distinguished from psychical interplay between already elaborated percepts, and the distinction cannot always be drawn on the basis of our ability to analyse a sense presentation by introspection. Two flickering images, each seen uniocularly, may be inextricably fused to form a single percept, and yet experiment has shown that the synthesis is a psychical one of two mutually independent uniocular percepts. The inability to separate the two by introspection is merely due to their simultaneity. But many examples of interaction on the physiological plane have been brought forward, and their further study promises greatly to advance our knowledge of the functions of the central nervous system in relation to sensory phenomena. In the past, far too little attention has been paid to such integrative mechanisms by most workers on the physiology of sense organs.

To quote again from Head [36, p. 741]: "The forms assumed by . . . sensation are ordered and predestined on the physiological level, as the result of innumerable integrations, which take place outside consciousness. These processes are not open to conscious analysis; it is only the interplay of sensations that can be discovered by introspection. The psychologist, who attempts to discover a strict psychophysical parallelism, ignores the central link of the problem. He assumes that the nature and conditions of the physical stimulus can be brought into direct relation with the psychical act of sensation. . . . This fundamental error vitiates much of the work on the psychology of the senses. It is only under artificial conditions that the physiologist can foretell exactly what reaction will follow a given physical stimulus; previous occurrences in the tissue may entirely change the nature of the response. Adaptation, biphasic activity, and facilitation form a normal part of the vital activity of the nervous system; they may intervene between a measured physical stimulus and the physiological effect, and make it impossible to establish a direct and immediate correlation. Therefore, between the impact of some physical force on the tissues of the body and the psychical act of sensation, are interposed reactions, which, in many cases, cannot be predicted. . . . At the periphery, we see how a measurable physical stimulus is transformed into various physiological reactions. At the other end we can observe the ultimate condition of these impulses, in the act of subserving sensation, after they have undergone integration and selection."

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OTITIC HYDROCEPHALUS.

BY C. P. SYMONDS, M.D.

It has long been recognized that symptoms and signs of increased intracranial pressure, including swelling of the optic discs, may occasionally occur as a complication of otitis media without the existence of a cerebral abscess, and may subside without surgical intervention. Thus Taylor [16] wrote in 1890, "It is important to remember what has now been verified in numerous cases, that in mastoid suppuration there is often double optic neuritis, with an entire absence of meningitis or of abscess, as proved by post-mortem examination, and by recovery after simple trephining the mastoid cells."

In certain of these cases signs may be present such as hemianopia, aphasia or hemiparesis, indicating a local disturbance of cerebral function corresponding with the usual situation of a cerebral abscess. Such cases, under the title of pseudo-brain abscess, or non-suppurative encephalitis, have been recorded by Adson [1] and Symonds [15]. In the majority, however, localizing signs are absent and the clinical picture is that of increased intracranial pressure alone. It is with these cases that the present paper is concerned. Quincke [14] appears first to have defined this group as one in which the signs of increased intracranial pressure were associated with a clear cerebrospinal fluid on lumbar puncture. In addition to otitis media, he recognized such causes as head injury, overwork, alcoholism and influenza. He considered the condition to be a benign form of meningitis, in which the choroid plexuses secreted an excess of fluid, and included it in his category of serous meningitis.

Warrington [17], in his paper upon "Intracranial Serous Effusions of Inflammatory Origin," published in 1914, reviewed the literature up to that date and added some observations of his own. He agreed with all the writers on the subject whose work he reviewed in regarding the condition as a form of meningitis, clinically benign, but with no clear line of distinction from the more severe and suppurative varieties. He regarded the meningitis as inflammatory and of infective origin, and noted otitis media as the commonest associated condition. He considered that although the cerebrospinal fluid might be normal, protein and cells might be increased, and the latter might be lymphocytes or polymorphonuclears or both. "The examinations of the cerebrospinal fluid are not inconsistent with the view that meningism, serous meningitis or ependymitis or sero-purulent meningitis are grades in an inflammatory process." He reported four cases in which symptoms of increased intracranial pressure with optic neuritis were associated with otitis media, and in which recovery occurred without any evacuation of pus from the brain. In two of these focal signs of cerebral involvement were present in the form of hemiparesis. In the other two cases (a boy of 13 and a man aged 54) the picture was that of simple intracranial hypertension. In none of them was the cerebrospinal fluid subjected to microscopic and chemical examination.

Appearing just before Warrington's paper, but unnoticed by him, Passot's thesis [13] dealt with the "méningites et états méningés aseptiques d'origine otique." This paper seems to have attracted less attention than it deserved. The author pleads for a classification of the non-purulent intracranial complications of otitis media upon the basis of a chemical and microscopical examination of the cerebrospinal fluid. A clear fluid may be obtained in two types of case. In the one type the clinical symptoms are those of a mild meningitis and the fluid contains an excess of cells and protein. In the other type the symptoms are those of increased intracranial pressure alone, and the cerebrospinal fluid, save for its increased pressure, is normal.

The former type may be fairly termed a serous meningitis; the latter, presenting neither clinical nor serological evidence of meningeal inflammation, is better called a hypertensive state. To this group (états méningés hypertensifs) he devotes nearly one-third of his paper.

The condition, he states, is commoner in children or adolescents than in adults; it often occurs in the course of a simple otitis media unassociated with any complications, and may be completely relieved by drainage of the cerebrospinal fluid. As a rule there is little osteitis, the roof of the antrum is intact and the dura mater under pressure, but of healthy appearance. On account of the benign course of the condition post-mortem evidence is scanty, but congestion of the choroid plexuses and œdema of the ependyma and sub-ependymal tissues have been reported. Operative observations show an excess of cerebrospinal fluid in the subarachnoid space and in the ventricles. At lumbar puncture the distinctive features, in addition to the clarity of the fluid, are its pressure and amount, both being greater than those obtained in an early meningitis. Microscopical and chemical examination invariably shows a normal cell and protein content. Clinically he distinguishes two pictures. The one is that of a simple increase of intracranial pressure. There is a progressive development of headache, drowsiness and papillœdema. Nausea and vomiting are uncommon. Meningeal symptoms are absent or rare. The temperature is not abnormal, the pulse, at first rapid, later becomes slow. The whole clinical picture is more like that of tumour or abscess than that of meningitis. Secondary optic atrophy and blindness may develop if the condition of increased intracranial pressure is unrelieved. This clinical picture Passot believed corresponded with an excess of fluid in the subarachnoid space rather than in the ventricles—a meningeal hydrops (hydropisie méningé). The evidence presented in favour of this assumption is that the increased intracranial pressure is relieved by lumbar puncture and that at operation, in one of the cases quoted, incision of the dura mater gave a free flow of cerebrospinal fluid, whilst puncture of the brain (depth not stated) was negative.

The alternative clinical picture, which he assumed to depend upon an internal hydrocephalus, includes a brief phase of headache and drowsiness, with subsequent development of hemiparesis or convulsive seizures of cortical type which may be unilateral or bilateral. Papillœdema and increased pressure of the cerebrospinal fluid at lumbar puncture are accessory phenomena and, if present, indicate the co-existence of meningeal hydrops. The development of this clinical picture may be acute or subacute. The spinal fluid in this (the hydrocephalic) as in the other (meningeal hydrops) variety is clear, and normal in its constituents. The treatment of these hypertensive states should be decompression by evacuation of spinal fluid. The condition being often associated with a simple otitis media, there is no special indication for intracranial exploration, nor even necessarily for a mastoid operation. The state of affairs is quite different from that which is obtained when a clear cerebrospinal fluid contains excess of cells and protein—" true serous meningitis "—the latter should be regarded as a preliminary or mild stage of purulent meningitis and treated accordingly by radical operative measures.

In meningeal hydrops drainage by lumbar puncture is sufficient. Often a single puncture will suffice, in which case the procedure which establishes the diagnosis effects a cure. In the condition of hydrocephalus ventricular drainage is necessary, either by way of the auricular wound or through a separate and clean field of operation in the subtemporal region. If operation on the one side fails to relieve the symptoms, the other ventricle should also be drained. This procedure is advised on the assumption that the hydrocephalus is obstructive, the result of adhesions obliterating the effluent channels from the fourth ventricle, and on occasion blocking the foramina of Monro.

Passot's observations seem to establish clearly the occurrence of a clinical picture of intracranial hypertension complicating otitis media, with a normal cerebrospinal fluid. His distinction between the two varieties of this condition—meningeal hydrops and hydrocephalus—appears to be less securely founded.

Aboulker [2] divides aseptic meningitis into diffuse and hypertensive forms. In the former the cerebrospinal fluid contains an excess of protein and of mononuclear or polymorphonuclear cells, and the sugar content is diminished. The latter is characterized by an excess of normal clear fluid, realizing a syndrome of hypertension slight or transient, or well-marked and persistent even after eradication of the bony disease and lumbar puncture. Finally, hypertensive meningitis may be localized in the subarachnoid space or the ventriclar cavities, that is to say, it may be external or internal.

Several good clinical examples are recorded in his paper, for instance, Case 17, that of a patient aged 20, who three weeks after a mastoid operation developed severe headache with low fever and bilateral papillœdema. At lumbar puncture the cerebrospinal fluid was under increased pressure but clear and with no abnormal constituents. The right temporal lobe was explored for abscess with negative result. The patient ultimately recovered. In three of the eight cases of hypertension which he records it is to be noted that recovery ensued after operative treatment of the initial lesion (otitis media, mastoiditis) without intracranial exploration.

Aboulker, in considering the differential diagnosis between the condition which he calls hypertensive meningitis and cerebral abscess, argues that in abscess the evolution of the symptoms is slow and often silent, headache is not a prominent symptom, papillœdema is uncommon, temperature is variable, the patient is often ambulant and when he takes to his bed is usually drowsy. In hypertensive meningitis the onset of symptoms is abrupt and the development rapid, headache is extremely severe, papillœdema is constant and often accompanied by hæmorrhages, the temperature is high, vomiting is frequent and the patient is confined to bed on account of the headache. He believes that the condition arises as a meningitis in which the initial meningeal symptoms are masked by those of severe hypertension. He argues that the clear normal cerebrospinal fluid encountered in this condition is indistinguishable from that met with in cerebral abscess. Therefore exploratory operation is necessary to establish the diagnosis. If the case is one of hypertensive meningitis, exploratory puncture of the temporal lobe instead of yielding pus will give a flow of clear fluid under pressure from the subarachnoid space or ventricle. The exploratory craniotomy should be carried out through a clean field without traversing the infected bone and superficial tissues. If an abscess be found the mastoid region can be opened up separately.

It will be noted that the clinical picture and cerebrospinal fluid findings as described by Aboulker correspond in the main with the observations of Passot. Aboulker, however, suggests that the condition of hypertension may develop from an initial phase of meningitis, and notes the occurrence of high fever. In one important point Aboulker's observation would appear to the writer to be at fault. The cerebrospinal fluid in cases of cerebral abscess, though it is almost always clear, always shows some increase of protein and almost always an increase of cells. Here therefore is a point of distinction which may be added to those which have already emerged in the differential diagnosis of cerebral abscess from a condition of intracranial hypertension due to a simple excess of normal cerebrospinal fluid.

Mygind [12], in a paper dealing with the benign forms of otogenic meningitis, states that in fifteen cases under his observation the cerebrospinal fluid remained clear. The fluid was frequently examined in a number of these cases and the pressure measured. On the clinical side four cases at no time showed any cervical rigidity; five had papillœdema, and two had sixth-nerve palsies.

Two of his observations are of particular importance in relation to the present discussion.

Case 2 of his series, a girl aged 17, developed symptoms of a mild meningitis with an acute otitis media. On the first day of observation the cerebrospinal fluid was clear but contained twenty-six lymphocytes per cubic millimetre. The pressure was 400 mm. of water. On the fourth day paralysis of the right sixth nerve was observed. The temperature gradually fell and the symptoms and signs of meningitis diminished, but on the seventh day slight swelling of the optic discs was noted. On the ninth day all neck stiffness had disappeared. On the sixteenth day headache and vomiting occurred. Lumbar puncture yielded a clear cerebrospinal fluid under the enormously high pressure of 950 mm. of water, clear and containing less than one cell per cubic millimetre. The patient continued with headache, vomiting and papillœdema up to 4D. in the right eye and 3D. in the left. The cerebrospinal fluid remained normal save for excessive pressure. The patient made a very gradual improvement without further treatment. Six months after the onset swelling of the discs was still present with a cerebrospinal fluid under a pressure of 600 mm. of water. The patient felt well, but "had a headache now and then."

Case 3 was that of a boy, aged 10, with a chronic left-sided otitis media who developed drowsiness, fever, a left sixth-nerve palsy and papillœdema. The cerebrospinal fluid was clear under a pressure of 600 mm. of water and contained two lymphocytes per cubic millimetre. Recovery ensued, but swelling of the optic discs was still present two months after the onset.

Ayala [3], in a briefly reported communication upon the type of case under discussion, emphasizes the need of distinguishing the condition of generalized hypertension from that which may result from a localized encysted meningitis (meningitis serosa circumscripta). Many cases of the latter have been reported in the posterior fossa simulating the picture of a cerebellar abscess (e.g., Jenkins [9], Caliceti [6], Ferreri [8], Baldenweck [4]). For the condition of generalized hypertension Ayala proposes the term ependymitis serosa rather than meningitis serosa.

Kobrak [10], apparently referring to the type of case under discussion, described the increased cerebrospinal fluid pressure with clear transparent fluid, associated with swelling of the optic discs, and records improvement after lumbar puncture. He dismisses the clinical picture, however, as that of meningitis.

Leidler [11] describes a case in which, following a right-sided mastoid operation with lateral sinus infection and ligature of the internal jugular vein, the patient developed severe headache and papillœdema lasting several weeks with ultimate recovery, and suggests that the state of increased intracranial pressure was due to obstruction to the venous outflow. Claude and Lamache [7] record three cases of so-called serous meningitis simulating cerebral tumour. One occurred in a woman with chronic otitis media. Symptoms of increased intracranial pressure, including papillœdema, were present. Recovery followed lumbar puncture.

Cairns [5], under the heading arachnoiditis (serous meningitis), states that the clinical syndrome under discussion appears after acute or chronic mastoiditis, especially when the labyrinth has been infected. He remarks that "the main clinical feature is papillœdema, often of extreme degree, and the headache and other general symptoms may be so slight that the condition is not recognized until sight is seriously impaired." He reports a single case in full, that of a boy of 5, in whom an incomplete left mastoidectomy was first performed. During convalescence there was slight fever and vomiting. Six months later otorrhœa recurred and was associated with vomiting. The cerebrospinal fluid at that time was recorded as clear, under pressure, no cells, protein 0·02 per cent. The left mastoid was opened and further excavated. The left temporal lobe was explored with a needle and no abscess found. During convalescence attacks of headache and vomiting occurred, but he eventually left hospital apparently well. Two months later deterioration of vision was noticed, and the ophthalmoscope revealed severe papillœdema and optic atrophy. The cerebrospinal fluid pressure was 230 mm. of water; the fluid was clear, sterile, and contained one cell and 0·02 per cent. protein. Cairns refers to two similar cases in which the papillœdema reached 4D. and 2D. respectively, in which perfect recovery occurred with normal vision without any treatment at all. He suggests that the condition is one of hydrocephalus due to increased formation or defective absorption of cerebrospinal fluid, or both.

My first experience was with a case under the care of Mr. T. B. Layton at Guy's Hospital. Mr. R. Cann, who was jointly responsible with Mr. Layton for the operative treatment, has kindly provided me with the notes:—

Case 1.—*Male, aged* 12 *years. Chronic suppurative otitis media (right). Mastoiditis. Meningitis. Lateral sinus thrombosis. Headache. Papillœdema and right sixth-nerve palsy. Exploration of right temporal lobe with discovery of internal hydrocephalus. Fluid obtained from ventricle normal. Complete recovery.*

Albert C., aged 12, had chronic suppurative otitis media of the right ear since 4 years old, following measles. He was admitted to Guy's Hospital, April 28, 1928, complaining of pain over the right mastoid, vomiting and drowsiness.

On admission.—Temperature was 102·6° F., the pulse 84, and respiration 20. He appeared sallow, drowsy and ill. His tongue was dry and furred. He was tender over the right mastoid and had discharge from his right ear. The central nervous system was normal.

April 28, 1928: Operation.—The mastoid was opened and pus was found in the small antrum and in the cells. Pus in the lateral sinus groove was released, displaying a collapsed lateral sinus. On further removal of bone to expose the dura beyond, the lateral sinus filled spontaneously. The dura of middle fossa when exposed appeared normal. The wound was left open.

April 29: Temperature 104·4° F., pulse 100. He complained of frontal headache. The right external rectus muscle was paralysed. There was marked photophobia and rigidity of his neck, and Kernig's sign was positive. The abdominal reflexes were normal, but the knee-jerks and ankle-jerks were not obtained.

Diagnosis: Meningitis.

April 30: Temperature was 100°-103° F. Taking fluids well. His state was otherwise unchanged.

May 2: Temperature was lower, 99° to 100° F. There was pain and tenderness over the right sterno-mastoid muscle and some torticollis. Photophobia was still marked. He was restless and cried out during the night.

May 5: Condition unchanged. At 10 p.m. he had a rigor, the temperature rising to 106° F.

Diagnosis: Lateral sinus thrombosis.

May 6: Operation.—The right internal jugular vein when exposed in the neck was found collapsed and was ligatured. The mastoid wound was opened up. The lateral sinus was incised and contained pus. The exposure was prolonged backwards till free bleeding was obtained. The wound was packed.

May 9: Temperature oscillating to 103° F. The patient felt and looked better. The tenderness of the sternomastoid had gone and the rigidity of his neck was less. Photophobia and strabismus were unchanged.

May 12: Temperature 104·8° F. Complained of frontal headache. Examined by Dr. Symonds, who reported: "Marked papillœdema of both discs. The fields were full. The right external rectus was paralysed. The left abdominal was absent. The plantar responses were flexor. Kernig's sign was doubtful. Cerebellar tests were negative." He considered that in view of the marked swelling of the discs there was probably an intracranial abscess. In view of absence of cerebellar signs and paralysis of right sixth nerve, the probable localization was in the middle fossa and not in the posterior. In view of the sudden rise of temperature, immediate exploration of the brain was advised.

Operation.—On exposure of the middle fossa above the mastoid the dura appeared normal. The first puncture upwards with needle and syringe gave a flow of cerebrospinal fluid under tension at a depth of 5 mm., that is evidence of a dilated lateral ventricle, presumably due to internal hydrocephalus. Exploration backwards and forwards was negative. Exposure of posterior fossa behind the lateral sinus and exploration of the cerebellum in three directions gave no results.

Report on cerebrospinal fluid, from ventricle: A few red cells but no white cells. Protein 0·03 per cent. Cultures sterile.

May 14: Temperature oscillating to 104° F. Free drainage of cerebrospinal fluid continues from the wound.

May 19: Temperature was lower. General condition improving. He had occasional headache. Photophobia and paralysis of sixth nerve were unchanged. Very wasted.

May 23: Temperature normal. Examined by Dr. Symonds. Papillœdema was still very marked. The right sixth nerve was still paralysed. The plantar responses were extensor, but the other reflexes were normal. There was slight spasticity of the limbs.

May 29: Temperature remains normal. Patient was much better and the wound was healing well.

June 4: Examined by Mr. Morgan. "Both eyes show papillœdema, probably subsiding, with swelling of 3, 5 to 4 diopters. He will probably develop secondary atrophy of the nerves."

June 9: Up on couch.

June 16: Up on chair. The wound was almost healed. Some strabismus was still present.

August 28: Returned from convalescent home. There was slight discharge from the right ear. The wound was healed. Sight was good and strabismus had disappeared.

October 28: There was slight discharge from the right ear, but no other complaints. Returned to school.

Mr. Cann informs me that the patient remains well at the time of writing.

Lumbar puncture in this case as a preliminary to the intracranial exploration of May 12, 1928, would probably have revealed a normal cerebrospinal fluid (judging from that obtained by ventricular puncture). Had this been disclosed the possibility of a cerebral abscess would have appeared remote, and it is highly probable that the patient would have made an equally good recovery with (or perhaps without) lumbar puncture, and without being exposed to the risk of an additional and unnecessary operation.

Case 2.—*Female,; aged* 10 *years. Acute otitis media* (*left*) *with fever for one week. During the subsequent month occasional symptoms such as shivering, nausea, giddiness and suboccipital pain. Frontal headache. Diplopia. Six weeks from onset of illness bilateral papillœdema and left sixth-nerve palsy. Cerebrospinal fluid normal save for increased pressure. Mastoid explored, no definite osteitis found. Complete recovery without further treatment.*

Clarice M., aged 10, was seen with Mr. Mollison on September 18, 1928. The history in this case was supplied by the child's nurse, an excellent observer.

July 28, 1928: Acute left earache, followed by discharge after one day. The earache did not entirely disappear. The temperature remained up for a week.

August 5: Woke at 4.30 a.m., shivering and complaining of nausea and giddiness. Next day was better.

August 13: She was away to France on summer holiday, apparently well.

August 15 : Sudden attack of nausea ; seemed to lose her senses momentarily ; later she vomited and complained of stiffness in the left side of the neck and pain in the left ear. She remained in bed for four days continuing to complain of pain in the left suboccipital region, and could not turn her head to the right without also twisting the shoulders.

August 27 : She was well and started sea bathing.

September 5 : She complained that the sunlight upset her and later that she had double vision. From this time onwards, in addition to continued diplopia, there was complaint of occasional attacks of frontal headache, nausea and giddiness.

September 17 : On account of her eyesight she was taken to see Mr. H. L. Eason, who discovered a paresis of the left sixth nerve and well-marked papillœdema on both sides. Mr. Mollison saw her the same day and noted : "The left membranum tympani was a little red, the right normal."

September 18 : The writer noted : She was mentally alert and excitable. There was no aphasia to rough examination. Visual fields were full to rough tests. There was well-marked papillœdema with hæmorrhages in both eyes. The left pupil was larger than the right, but both reacted normally. The ocular movements were full, except for paresis of the left external rectus. No nystagmus was observed. The corneal reflexes were brisk and equal. The other cranial nerves were normal. There was no defect of postural sense and no astereognosis. No weakness, wasting or inco-ordination was present. The arm-jerks, knee-jerks and ankle-jerks were present and equal, the abdominal reflexes were equal, and the plantar responses were flexor.

In walking she was at first unsteady, with no special tendency to fall in any direction. Heel-and-toe walking was good. No abnormal posture was noticed.

The other systems were normal. The neck was not stiff and Kernig's sign was not present.

Provisional diagnosis : Probably left cerebellar abscess.

September 19 : Mr. Eason examined the visual fields on the perimeter and found the peripheral fields full with slight enlargement of the right blind spot ; visual acuity was $\frac{6}{6}$ on both sides.

September 20 : Lumbar puncture gave a clear fluid, which rose rapidly to the full height of the manometer of water and overflowed—a gross increase of pressure. Dr. Greenfield's report was as follows :—

Cerebrospinal fluid	Clear, colourless, no coagulum.
Cells	Less than 1 per c.mm.
Total protein	0·03 per cent.
Globulin	Nonne Apelt and Pandy reactions negative.
Glucose	0·081 per cent.
Chlorides	0·75 per cent.

This fluid appears to be quite normal.

In view of this report the writer withdrew his provisional diagnosis of cerebellar abscess and considered the possibilities to be either a hydrocephalus secondary to the otitis, or a purely coincident mid-cerebellar tumour. In consultation with Mr. Mollison it was decided that the mastoid should be explored.

September 21: Mr. Mollison operated on left mastoid and found: Bone very vascular but no pus; the dura mater was under increased tension, more in the posterior than the middle fossa, and possibly pinker than normal.

October 6: No complaint of headache. Wound was healed and there is no discharge from the ear. Last evening she had an attack in which she suddenly said that everything seemed to be a long way away and then thought she was going to die. The whole episode lasted only a few minutes.

On examination: There was no aphasia to careful tests. Optic discs were about as swollen as before. The visual fields were normal to rough tests. The left pupil was larger than the right. There was no nystagmus in any direction, and no other disturbances in the cranial nerves. There was no weakness, wasting, inco-ordination or abnormality in the tone of the muscles, and no defect of sensation.

The arm-jerks were not obtained, but the knee- and ankle-jerks were present and equal. The right plantar response was a little indefinite, the left flexor. The abdominal reflexes were present and equal. No neck stiffness or Kernig's sign.

The child rapidly proceeded to make a complete recovery, and a note from her doctor states that she has remained in perfect health during the subsequent two years.

In this case the timely examination of the spinal fluid undoubtedly saved me from advising an exploration of the cerebellum. A cerebellar abscess giving rise to such a degree of hydrocephalus would certainly have been associated with some increase of protein and cells in the fluid. Apart from this, however, the fitness of body, alertness of mind, slightness of symptoms and absence of localizing signs in association with advanced papillœdema combined to form a clinical picture unlike that of a cerebellar abscess.

The case conforms to the clinical picture already described in the literature, and bears out the contention of Passot that the condition of increased intracranial pressure may follow an acute and apparently uncomplicated otitis media. But a critical analysis of the evolutionary phase leads me to suppose that the occasional symptoms of nausea, fever, suboccipital pain or giddiness which occurred during this time were the expression of a quiet extension of the infective process from the middle ear to the meninges.

Case 3.—*Female, aged* 13 *years. Chronic suppurative otitis media (right). Cortical mastoid operation at* 7. *Recent otorrhœa. Formation of sinus in mastoid scar and evidence of zygomatic osteitis. Operation with removal of diseased bone and exposure of dura. Meningitis with cloudy cerebrospinal* *fluid. Extradural abscess found in middle fossa and drained. Recovery from meningeal symptoms. Development of headache and papillœdema. Cerebrospinal fluid normal save for increased pressure. Complete recovery after repeated lumbar puncture.*

Winifred B., aged 13, was admitted to the Central London Throat, Nose and Ear Hospital, under Mr. Gill-Carey, on February 20, 1930. The house surgeon's notes state: Right cortical mastoid performed six years ago. Tonsils and adenoids removed five years ago. A week ago complained of pain in the ear; on the following day there was discharge from meatus with relief. The discharge lasted one day; she then developed swelling over the mastoid. On examination a sinus was found over the right mastoid scar; slight mastoid tenderness; pus in meatus; membranum tympani perforated and discharging pus. Hearing on the right was reduced to a faint whisper at 3 ft., on left normal. She was discharged on February 25, but readmitted on March 1, with œdema and tenderness over the root of the right zygoma and a sinus over the mastoid scar which had broken down and was discharging. The meatus contained pus. There was sagging of the anterior meatal wall. The left ear was normal.

March 1, 1930: Operation by Mr. Gill-Carey; reopening of the mastoid which was converted into an epitympanic mastoid. The mastoid cortex was cellular, the old antral cavity was partially filled with new bone and granulations. The tip of the mastoid, which had not previously been cleared, was removed; it contained infected cells. The lateral sinus was exposed. The bone at the posterior part of the fossa was necrotic. The dura of the middle fossa was exposed in two places and cells were traced forward into the zygoma; the bridge was cut through and the outer attic wall was removed. The incus and malleus were seen, but not removed. A meatal flap was cut. The cavity was packed and closed behind, except at its lower end.

Following the operation the temperature remained in the neighbourhood of 100° F. for a week, and rose again to 100° F. on March 14, and 102° F. on March 21, subsequently remaining high.

March 24: The patient complained of pain in her right ear and frontal headache, felt giddy and had nausea, but no vomiting. There was some retraction of her head, but Kernig's sign was negative. Slight spontaneous nystagmus was present to the left. She could hear conversational voice at 12 in. in the right ear with a noise box in the left. The cold caloric test was positive on the right. There was no dysdiadokokinesis, past pointing or weakness in her arms or legs.

March 25: 30 c.c. of spinal fluid was withdrawn by lumbar puncture; it was cloudy and under increased tension.

March 26: Operation by Mr. Gill-Carey. The right mastoid wound was reopened. The lateral sinus was further exposed, but appeared healthy. The dura of the posterior part of the middle fossa appeared healthy, but an extradural abscess was found in the temporal region with a sequestrum in the zygomatic region. A counter-incision was made in front of the auricle and a tube inserted. The remaining area was drained with Carrell-Dakin tubes. The temperature continued high until March 31, after which it remained normal.

March 28: Headache and neck rigidity. 25 c.c. spinal fluid which was withdrawn by lumbar puncture was cloudy and contained a great excess of leucocytes.

March 31: No further symptoms; lumbar puncture gave 25 c.c. of clear fluid.

April 4: Complained of severe headache, but there were no meningeal symptoms. By lumbar puncture 55 c.c. of clear fluid was withdrawn under marked tension. Pathological report: 80 cells per c.mm., 80 per cent. of which were lymphocytes and 20 per cent. polymorphs.

April 22: She remained well until two or three days ago, but since then has had severe headache which was more marked to-day, but there were no meningeal symptoms. By lumbar puncture 50 c.c. of clear fluid was withdrawn under definite pressure; the pathological report described it as normal.

April 24: She still complains of headache; by lumbar puncture 50 c.c. of clear fluid under definite tension was obtained.

April 26: The writer saw her and dictated the following note: "In the right eye there is papillœdema with hæmorrhages and 2 diopters of swelling. In the left ½ diopter of swelling. The visual fields are normal to rough tests. The right pupil is smaller than the left. The ocular movements are full; there is no nystagmus or diplopia. The corneal reflexes are equal and normal. There is slight left facial weakness and the palate moves to the right, but the tongue is protruded in the mid-line. The finger-nose-finger test is equal on the two sides; there is no dystonia.

"The arm-jerks cannot be obtained. The right plantar reflex is flexor, the left doubtful. The knee- and ankle-jerks are present and equal. The upper and lower abdominal reflexes are brisk and equal.

"The physical signs, so far as they go, are suggestive of a right temporal abscess, but I think her symptoms and signs *might* be explained by an internal hydrocephalus from adhesions as a sequel of the recent meningitis. I therefore advise watching and exploration of the right temporal lobe if symptoms of increased intracranial pressure develop."

The headaches gradually subsided and the patient left the hospital on May 17 apparently well. Her mother states in a recent letter that she has remained in perfect health and is doing well at school.

In the present state of our knowledge the clinical picture of advanced papillœdema, in association with a general state of physical fitness, an alert mind, the absence of any localizing signs, and a normal spinal fluid should have led to a more positive diagnosis of simple hydrocephalus in this case. The quantity of cerebrospinal fluid withdrawn—more than 50 c.c. on several occasions—suggests free communication between the needle and the ventricular system, and is better consistent with the hypothesis of over-secretion of fluid than any other.

The clinical picture in Case 1 of this series was complicated by the presence of high fever and illness, due probably to a septicæmia consequent upon the lateral sinus thrombosis. In the other two patients the general state of physical fitness and the alertness of mind were in marked contrast to the gravity of the illness, as it might have been judged from the ophthalmoscopic examination. Intermittent headache and papillœdema were symptoms common to all. In Case 1, and again in Case 2, a sixth-nerve palsy was noted on the side of the discharging ear. Apart from this there were no definite signs in any case of a focal lesion either of the brain or cerebellum. In Case 1 lumbar puncture was not performed, but the cerebrospinal fluid obtained from a ventricle at operation was normal. In Cases 2 and 3 lumbar puncture gave normal fluid under excessive pressure.

In Cases 1 and 3 there was a phase of the illness preceding that of increased intracranial pressure in which both clinical and serological evidence of meningitis was present. By the time, however, that papillœdema was noted the excess of cells and protein had disappeared from the cerebrospinal fluid (*cf.* Mygind, Case 2). In Case 2 of the present series the evidence of a preliminary phase of meningitis is less certain and dependent upon the clinical data only, but these are at least suggestive.

DISCUSSION.

From a review of the material collected in this paper, the writer is convinced that as a not very uncommon complication of otitis media there may occur a state of increased intracranial pressure due to the presence of an excess of normal cerebrospinal fluid. This condition, which has usually been described hitherto under the title of serous meningitis, but which shows no clinical or serological evidence of meningeal inflammation, is sufficiently constant in its manifestations to deserve a separate name. The term ependymitis serosa has already been proposed by Ayala, but implies a knowledge of the ætiology which we do not actually possess. The writer suggests "otitic hydrocephalus," a title which implies no active process of inflammation, and, being deprived of the qualification, internal or external, will include fluid both within the ventricles and the subarachnoid space.

The ætiology and pathology of the condition remain obscure. What slight evidence we possess suggests either an excessive secretion from the choroid plexus or a defective absorption through the arachnoid villi. The hypothesis of an obstructive internal hydrocephalus due to inflammatory occlusion of the effluent channel from the ventricles has also to be considered, but the high pressures recorded with the manometer and the large quantities of fluid withdrawn in several cases are against this explanation.

The condition appears almost confined to children and adolescents. It may occur as a complication of an acute or chronic otitis media with or without mastoiditis, labyrinthitis, lateral sinus thrombosis, extradural abscess, or meningitis.

Of the symptoms, in the fully-developed state of otitic hydrocephalus, intermittent headache and papillœdema are the most constant. A sixth-nerve paralysis on the side of the discharging ear has been recorded in a number of cases. The headache is generalized or occipito-frontal, and of the bursting type which characterizes increased intracranial pressure. It may be of severe or slight degree, and in the latter case papillœdema may advance to secondary optic atrophy without any other symptoms of importance. Nausea or vomiting may be associated with the headache, but are inconstant. The temperature and pulse-rate in the fully-developed state are normal. Drowsiness may sometimes be present, but on the other hand the mental state may be remarkably clear considering the degree of papillœdema.

The evolution of the symptoms may be insidious, or they may develop after a preliminary phase of fever and cervical rigidity, indicating a meningitis. In this case the symptoms of meningitis subside as those of hydrocephalus develop.

The cerebrospinal fluid in the fully-developed state is under increased pressure, but clear and contains no excess of cells or protein. In those cases in which there is a preliminary phase of meningitis, the cerebrospinal fluid examined at this stage shows an excess of cells and protein.

The course of the illness may be protracted to weeks or months, but leads towards complete recovery. This, however, may be complicated by impairment of vision from optic atrophy.

Although in some cases recovery appears to have been spontaneous, the rational line of treatment is drainage of the excessive cerebrospinal fluid by lumbar puncture. This should be repeated if necessary, the indications being recurrent headache or persistent papillœdema. If repeated lumbar puncture fails to relieve the symptoms, ventricular puncture should be undertaken, in the first place on the right side whatever the side of the aural lesion. If right-sided ventricular drainage should fail to be effective in relieving symptoms, the left ventricle also should be tapped.

Surgical attention to the otitis media and its local complications plays a natural part in the treatment, but the presence of hydrocephalus is no indication in itself for intracranial exploration.

The differential diagnosis from cerebral abscess in the early stages of otitic hydrocephalus may be a matter of considerable difficulty, especially if a preliminary phase of meningitis has caused, for the time being, an excess of cells and protein in the cerebrospinal fluid. In the fully-developed state the main distinguishing features may be tabulated as follows:—

	Otitic abscess	Otitic hydrocephalus
Age	Any age	Almost always children and adolescents
General condition	The patient complains of malaise and appears ill	Between the attacks of headache the patient feels and looks well
Fundi	Often normal: if papillœdema is present it is of slight degree	Papillœdema constant: usually measurable swelling with hæmorrhages and exudate
Localizing signs	A right-sided temporal lobe abscess may be relatively silent: a cerebellar or left temporal abscess usually gives rise to characteristic localizing signs	No localizing signs are present. A sixth-nerve paralysis on the side of the lesion is present in a fair number of cases. Rarely unilateral or bilateral convulsive seizures may occur, or the plantar response on one or both sides may be extensor—the result presumably of increased intracranial pressure
Cerebrospinal fluid	Clear, pressure moderately increased, protein content constantly above normal, cells nearly always increased, mainly lymphocytes with an occasional polymorph	Clear, pressure often above 300 mm., quantity abundant, no excess of protein or cells

I have to acknowledge thanks to my surgical friends for permission to publish notes of the cases under their care, and to Mr. T. B. Layton, in particular, for constantly stimulating my interest in such clinical problems as have been approached in this paper.

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GLYCOSURIAS OF CEREBRAL ORIGIN.

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In recent years the extrapancreatic glycosurias have become a problem of the greatest interest on account of both the clinical and experimental investigations dealing with this problem. Especially has our knowledge of the benign glycosurias, which after all are not so very rare, made it necessary to try to find a pathogenetic classification on which to base a division of the different forms of glycosuria.

The division generally used is a purely practical, clinical one, namely, benign and non-benign glycosurias; pancreas-diabetes being counted among the latter, whilst the former generally are impossible to classify further. As regards anomalies in the sugar-metabolism which have a neurogenic, especially a cerebral cause, their existence has for a long time been clear, and in 1898 Naunyn analysed their clinical forms. The special knowledge which we have gained of late on this question has been derived from the study of epidemic encephalitis and from the experimental investigations which have been carried out concerning the influence of the hypothalamus and the corpus striatum on metabolism, these being the regions of the brain commonly affected by this disease.

The experimental investigations of Aschner, Camus and Roussy, Dresel and Lewy, Bailey and Bremer and others tend the same way as the famous sugar-puncture experiments of Claude-Bernard.

These experiments have shown that it is highly probable that, besides a centre in the medulla oblongata, there is also a centre for sugar regulation in the hypothalamus, and perhaps also others in the corpus striatum and the cerebellum. Following epidemic encephalitis anomalies in the metabolism, including sugar metabolism, are well known, and in some cases the latter have included glycosuria like that of diabetes mellitus (Moewes, Umber and Rosenberg). In epidemic encephalitis, as in other extrapyramidal diseases, it has also been possible to demonstrate disturbances in the sugar metabolism (Kasanin and Grabfield, Thatschew and Axenono).

Lastly, there is an anomaly of sugar metabolism which, according to John, often closely resembles diabetes mellitus, and which is perhaps due to cerebral dysregulation, namely, the diabetes of acromegaly.

The cerebral mechanism of sugar-metabolism regulation has, therefore, as has been pointed out by Binswanger, Kraus and others, assumed a prominent position amongst the problems relating to both normal and pathological metabolism, not least the sugar-metabolism.

In a paper [16] on the sugar content of the spinal fluid and its relation to adrenalin hyperglycæmia, I have dealt with these questions in detail, and have advanced the view that whilst a simple glucose hyperglyæmia does not, or only very slightly, influence the amount of sugar in the lumbar part of the spinal fluid, this amount is decidedly increased about two and a half hours after an injection of adrenalin, provided the blood-sugar rises enough (to about 0·150 per cent.). Under normal circumstances the increase is about 0·020 per cent. (e.g., from 0·050 per cent. to 0·070 per cent.).

In cases of disease in the so-called extrapyramidal system this increase is diminished or absent. From this I infer that an abnormally small increase in certain cases may of itself indicate a diseased condition of this part of the brain, even when no morbid condition is clinically manifest. The test itself I have called A-L-S-R (adrenalin-liquor-sugar-reaction), and a rise in the spinal fluid sugar of less than 0·015 per cent., or more than 0·030 per cent., corresponds to a reduced or increased A-L-S-R.

An increased A-L-S-R seems to occur in extrapyramidal diseases as well as in more common diseases of the brain.

I have made experiments with the A-L-S-R in some few cases with different anomalies of the sugar-metabolism.

The results may be seen in the following table.

In the main the results show that in seven cases in which the central nervous system was believed to be affected, there was also a reduced A-L-S-R, this pointing towards a localization of the nervous disease in the extrapyramidal system.

In three cases of true diabetes mellitus, the A-L-S-R was found to be increased.

In one case, probably a glycosuria of cerebral origin, there was also an increase (13).

In two cases the A-L-S-R was normal (11-12).

Furthermore, it was found that the increase was very small when the reaction was carried out on patients whose fasting blood sugar was increased (17-21).

Table showing Results of A.L.S.R in Patients with

No.	Fasting blood-sugar per cent.	Blood-sugar maximum per cent.	Time for a blood-sugar maximum to administration in minutes	Blood-sugar per cent. at time of puncture	Quotient per cent.	Spinal fluid sugar per cent I	Spinal fluid sugar per cent. II
	Group. I—A.L.S.R. in patients with normal fasting blood-sugar. (*a*) Reduced rise.						
1	0·107	0·157	30	0·081	54	0·058	0·058
2	8-10 0·090	0·202	95	0·163	—	—	0·068
	1-12 0·081	—	—	—	88	0·071	-
3	0·087	0·167	45	0·100	65	0·056	0·060
4	0·097	0·246	60	0·191	72	0·070	0·076
5	0·076	0·174	60	0·117	78	0·060	0·068
6	0·120	0·276	60	—	—	—	0·085
	0·098	—	—	—	63	0·062	—
7	0·085	0·210	60	0·169	80	0·068	0·082
	Group I.—(*b*) Increased rise and normal rise.						
8	0·116	0·344	105	0·112	70	0·082	0·112
9	0·107	0·301	90	0·263	68	0·073	0·111
10	0·089	0·273	85	0·236	76	0·068	0·114
11	0·103	0·211	70	0·102	58	0·060	0·077
12	0·100	0·291	90	0·289	77	0·077	0·102
13	0·100	0·211	60	0·153	60	0·060	0·094
	Single punctures.						
14	0·070	0 245	60	0·195	—	—	0·081
15	0·067	—	—	—	84	0·056	—
	0·081	0·218	65	0·168	—	—	0·082
16	0·105	0·256	60	0·194	—	—	0·089
	Group II.—Examination of A.L.S.R. in patients with increased fasting blood-sugar.						
17	0·155	0·257	60	0·257	70	0·108	0·110
18	0·158	0·267	110	0·245	—	—	0·119
			Percentage quotient, calculated from fasting blood-sugar				
19	0·236	0·293	55	0·266	51	0·119	0·122
20	0·166	0 348	55	0·264	86	0·143	0·143
21	0 222	0·349	115	0·301	—	—	0·160
			Percentage quotient, calculated from fasting blood-sugar				

ANOMALIES IN THEIR CARBOHYDRATE METABOLISM.

Time from administration until puncture in minutes II	Rise	Administration	Diagnosis
145	0·000	Glucose and adrenaline	Spastic paraparesis (congenital ?). Intermittent glycosuria
135	—	,, ,,	
Rise calculated	0·010	,, ,,	Renal diabetes, diabetic chart. Psychosis
140	0·004	,, ,,	Transitory glycosuria ; neurotropic gangrene
160	0 006	,, ,,	Arteriosclerosis cerebri, glycosuria, hyperglycæmia
140	0·008	,, ,,	Schizophrenia ?
135	—	— —	Glycosuria
Rise calculated	0·009	,, ,,	Hyperglycæmia intermittens. Psychosis
135	0·014	,, ,,	Pseudo bulbar-paralysis. Transitory glycosuria
150	0·046	,, ,,	Diabetes mellitus
150	0·038	,, ,,	
125	0·030	,, ,,	
145	0·017	,, ,,	Dementia organica. Glycosuria
130	0·025	,, ,,	Degeneratio psychopatica. Hyperglycæmia. Glycosuria
150	0·034	,, ,,	Epilepsia. Idiotia. Glycosuria
140	—	,, ,,	Renal diabetes. Psychosis
Rise calculated	0·022	— —	
135	—	,, ,,	Diabetes mellitus ?
165	—	,, ,,	Diabetes mellitus ?
125	0·002	,, ,,	Glycosuria intermittens. Psychosis
200	—	,, ,,	Diabetes mellitus ?

and the spinal-fluid sugar found = 75.

120	0·003	,, ,,	Diabetes mellitus ? Psychosis
210	0·000	,, ,,	Diabetes mellitus ? Psychosis
160	—		Diabetes mellitus ?

and spinal-fluid sugar found = 72.

In some few of the cases examined the results were uncertain, because a double puncture had not been carried out, but only one spinal puncture at the end of the experiment.

Lastly, in some cases it was found that the proportion between the sugar in the blood and in the spinal fluid was increased. The proportion, the percentage quotient $\left[\frac{\text{spinal-fluid sugar} \times 100}{\text{blood-sugar}}\right]$ normally is between 50 and 70, and when in some cases of anomalies in the carbohydrate metabolism it is found to be increased, this is perhaps due to special metabolic conditions. The main point in the investigations is, however, the difference which is found between the seven cases of glycosuria of cerebral origin and the three cases of diabetes mellitus.

In the first seven cases we find conditions which point towards a disease of the extrapyramidal system. Now, the question is whether the three cases of pancreatic diabetes also may be interpreted as expressive of changes in the regulating centres.

The probable existence of a correlation between the peripheral organs and the extrapyramidal system is well known. Both clinical and pathologico-anatomical observation indicate this. Also the fact that an area of the hypothalamus in fœtal life joins the entodermal tissue, forming the hypophysis, causes us to " suspect an intimate relation" between this part of the brain and the visceral functions (Ingvar and Petrén). Thus there seem to be numerous indications in favour of the supposition that a primary pancreatic diabetes in one way or another may cause changes in the "extrapyramidal system," or that perhaps these changes arise as related phenomena.

It is therefore natural to seek the genesis of the increased rise in the sugar in the changes in the brain, the more so as an increased A-L-S-R is a well-known phenomenon in several cerebral diseases.

It is possible that by means of this method of examination (A-L-S-R) we may be able to advance another step in the pathogenetic division of the different forms of glycosuria.

The material in hand is too small to allow of a definite judgment. But at any rate the A-L-S-R ought to be tried upon a larger and a clinically more diverse material.

The following case history may throw some light upon these matters and upon the related pathophysiological problems :—

Case 1.—A married woman, aged 51, admitted to the Neurological Department of the Rigshospital (January 7 to March 9, 1930).

Diagnosis : Tumour of the corpora quadrigemina.

History: Ill for past seven years. Initial symptoms were periods of tiredness, giddiness and breathlessness. Subsequently walking became difficult and vision failed. Has been bedridden for past six months. No history of lethargy.

On examination: V.A. $\frac{2}{36}$ R., $\frac{2}{24}$ L. Moderate, sharply outlined atrophy of both discs. Concentric restriction of both fields of vision. Hearing normal.

Cranial nerves: Pupils equal, but irregular, react poorly to light, but normally to convergence. Associated paresis of upward movement of eyes but upward movement occurs when the lids are closed. No other pareses. Nystagmus in all directions, especially on attempted upward movement.

Motor system: Slight ataxy of upper limbs, especially of right. Bilateral dysdiadochokinesis. Marked ataxy of lower limbs. Gait: walks with wide base and unsteadily. On walking there is a coarse tremor of head, trunk and limbs. Rombergism present.

Sensory system: All forms of sensibility normal.

Reflexes: All tendon-jerks increased on both sides, and both plantar responses of Babinski type.

Spinal-fluid: protein (after Bisgaard), globulin 2, albumin 40; cells 5/3 per mm.^{3}; Wassermann reaction, negative; percentage quotient, 63; A-L-S-R, 0·009 per cent.

Wassermann reaction of blood, negative.

Blood-pressure: 165/90.

X-ray examination of cranium: nil abnormal.

Urine: January 8, no albumin, no pus, sugar present.

January 9: Glucose in urine, twenty-four hours, 1·5 per cent. Neither acetone nor aceto-acetic acid.

January 11: Glucose in urine, twenty-four hours, 1·6 per cent.

January 15: Glucose in the morning specimen, 0·5 per cent.

Blood-sugar (fasting): January 11, 0·089 per cent.

After some days of antidiabetic treatment, the urine no longer contained sugar, and after a slight restriction in the amount of carbohydrates in the food there was no glycosuria during the rest of the patient's stay in hospital.

December 31: Determination of sugar threshold:—

9·40	a.m.	Blood-sugar (fasting)	0·086	per cent.	urine, no sugar, 25 grm. glucose and 300 gr. water
9 45	,,	,,	0·097	,,	
9·50	,,	,,	0·097	,,	
9·55	,,	,,	0·125	,,	urine, no sugar
10·5	,,	,,	0·143	,,	
10·15	,,	,,	0·132	,,	
10·35	,,	,,	0·132	,,	
10·45	,,	,,	0·132	,,	
11·00	,,	,,	0·125	,,	with sugar (slight reaction)
11·25	,,	,,	0·114	,,	

Sugar threshold: > 0·132 per cent.
< 0·143 ,,

December 25: The urine contained sugar half an hour after subcutaneous injection of 0·5 c.c. pituitrin (P.D. and Co.). This glycosuria lasted about eight hours. During the first two hours after the injection the blood-sugar did not rise above 0·123 per cent.

December 27: Experiment repeated with the same results.

During the previous days, and after these examinations, the patient's urine did not contain sugar.

February 20—Strauss' water test:

7.30 a.m.	.. ..		1,000 c.c. water	
8.30 ,,	.. ..	diuresis:	225 c.c.	specific gravity 1009
9.30 ,,	.. ..		300 c.c.	,, ,, 1004
10.30 ,,	.. ..		100 c.c.	,, ,, 1001 (minimum)
11.30 ,,	... ..		155 c.c.	,, ,, 1002
		7 hours	780 c.c.	
1.30 p.m.	.. ..		80 c.c.	,, ,, 1007
3.30 ,,	.. ..		63 c.c.	,, ,, 1007
February 21:				
7 a.m.	.. ..		225 c.c.	,, ,, 1011 (maximum)
		Total in 27 hours	1,178 c.c.	

Examination of the urine-filtration after Rehberg gave the following results:—

During one period the infiltration of urine was 762 c.c. per minute through the glomeruli; blood-sugar, 0·166 per cent.; therefore, in the same period the "filtrated" sugar was 269 mg. per minute; at the same time the secretion of sugar in the urine was 23·5 mg. per minute. The reabsorption of sugar in the tubuli was thus: (269—23·5): 275 mg. Normally (with a threshold of about 0·180 per cent.) the reabsorption ought to be about 300 mg., which gives us a deficit of about 55 mg. per minute.

The following period showed: Urine-filtration, 162 c.c. per minute; blood-sugar, 0·170 per cent.; filtrated sugar, 267 mg. per minute; sugar in urine, 31 mg. per minute; sugar reabsorbed, 263 mg. per minute. Deficit, about 65 mg. per minute.

The diagnosis of tumours in the corpora quadrigemina and the third ventricle may be difficult (Cartex and Camauer, Fulton and Bailey, Glaser). The symptoms are manifold and vary greatly from one case to another. Of special importance are the ocular symptoms, chiefly the loss of upward movement, together with changes in the discs, and hypothalamic and cerebellar symptoms.

In the above-mentioned patient, the symptoms indicate the presence of a tumour. The most important and decisive focal symptom was the conjugated ocular paresis, which definitely indicates a lesion of the superior corpora quadrigemina.

In order to understand this patient's glycosuria, it will be necessary to speak shortly of the theories on the function of the kidney which are at present prevailing.

As we know, it is Cushney who has founded the modern theories of renal function. According to Rehberg's modification of this theory, the formation of the urine takes place in the following manner: The so-called ultrafiltrate, a fluid of the same composition as the plasma, is pressed out from the blood through the glomeruli. As the ultrafiltrate passes through the tubules, water is reabsorbed to the blood. Through this reabsorption a difference arises between the concentration of the substances in the blood and in the tubular fluid, and therefore also a difference in the osmotic tension. Consequently, the substances in the tubular fluid tend to return to the blood. The influence of the physical-chemical laws, however, decides to what degree this is possible for each substance; some of them diffuse back quickly and completely until a balance is obtained, others do so to a smaller degree, and, lastly, some of them, e.g., creatinin, do not diffuse back to the blood at all, but remain in the tubular fluid, and therefore in the urine, in the same concentration as in the original ultrafiltrate in the glomeruli.

But, as far as some substances, e.g., chlorine and sugar, are concerned, an active reabsorption takes place. Under normal circumstances this reabsorption is complete as regards sugar, so that the urine contains no sugar. If now the content of sugar in the blood is sufficiently increased, this may cause the ultrafiltrate to contain so much sugar that the reabsorption is no longer effective, resulting in sugar in the urine, i.e., a glycosuria. The degree of hyperglycæmia at which the ultrafiltrate contains so much sugar that the reabsorption of the tubular cells no longer is able to remove it completely, is what is called the sugar threshold. According to Rehberg, only substances which are actively reabsorbed in the tubules can be counted among the threshold substances proper.

The amount of the filtration through the glomeruli may be determined by a method worked out by this author. As has been mentioned, the whole amount of creatinin contained in the ultrafiltrate will be excreted with the urine, as this substance is not able to diffuse back through the tubules. If, after administration of creatinin, the amount of creatinin in the blood and in the urine excreted and also the amount of the urine, are determined for a certain period, it is possible to calculate how much creatinin has passed from the blood through the glomeruli in this period, and from this the amount of the filtration may be calculated. By a simultaneous administration of glucose and quantitative determination of the glucose in blood and urine, it is possible to calculate the amounts of filtrated and reabsorbed sugar.

Such an examination has been carried out on the patient mentioned here. It appeared that the power of reabsorbing sugar was considerably reduced; this agrees with the value of the sugar threshold which was found.

As regards the reabsorption function of the tubules, it is known that, as far as chlorine is concerned, it depends on the secretion of the hypophysis, which restrains reabsorption, a decrease in the secretion of the hypophysis increasing reabsorption of chlorine (Starling and Verney).

Cerebral glycosuria may arise: (1) Through a dysregulation in the rise of the blood-sugar after the reception of carbohydrates, the result being an alimentary hyperglycæmia, on account of which the threshold is exceeded. (2) The threshold falls, i.e., the reabsorption of the sugar in the tubuli is reduced. In both cases the urine will contain sugar.

There are three possibilities of the origin of the last form of glycosuria: (1) Direct nervous influence upon the parenchyma of the kidneys. Such an influence has, however, never been proved directly. (2) Indirect influence through the vasomotor nerves. This influence most likely acts on the glomeruli. In the patient in question the examinations which were carried out showed nothing which points towards an impairment of the function of the glomeruli. (3) Centrally regulated, hormonal influence upon the kidney. It may be this which was responsible for the glycosuria of our patient.

It is indeed possible that a tumour in the region of the corpora quadrigemina directly or indirectly influences the nervous tissue round the third ventricle, which according to Spiegel and others is closely related to the hypophysis. We may infer a disturbance of neurohypophyseal function, resulting in a reduction in the absorbing power of the tubules.

It is true that the tests showed a reduced power of concentration of the kidney. Therefore it cannot be excluded *a priori* that the glycosuria is due to simple primary renal disease. But, firstly, there were no other signs of such a disease, and, secondly, it is very rare for glycosuric conditions to be due to disease of the kidneys. It seems to me more likely also that the reduced power of concentration (i.e., the reduced power of water reabsorption on the part of the tubules) may be interpreted as a result of the disease of the brain.

Furthermore, in our patient it was found that excretion of sugar in the urine was caused by the injection of a small amount of pituitrin (0·5 c.c. pituitrin Medicinalco), an amount which does not generally cause glycosuria, and this glycosuria arose together with an increase of the blood-sugar which did not reach the value of the threshold as previously determined. Of course from what we have previously accepted it was to be expected that pituitrin would reduce the power of reabsorption and cause glycosuria at a lower threshold than previously determined.

Lastly, I will recall the physiological enlargement of the hypophysis which takes place during pregnancy, and of the not uncommon glycosuria that appears during pregnancy, a glycosuria which, according to Faber, is indeed caused by a low threshold, which after pregnancy again attains its usual level. In this case the low sugar threshold seems to be caused by a functional disturbance of the hypophysis.

Case 2.—A man aged 45. Admitted to Rigshospital, July 1, 1929.

Diagnosis: Encephalitic epidemica chronica; glycosuria.

History: Previously good health. Nil *ad rem* in family history. "Influenza" in 1918 and 1920. No history of nervous symptoms in these illnesses. Some years later had a period of diplopia lasting for five days. Two subsequent periods of diplopia, the last just prior to admission to hospital. For several years an increasing weakness of the legs with occasional "twitchings." Impairment of memory.

On examination: Cerebration slow, memory poor. Optic discs normal. Slowly reacting pupils. No diplopia. Nystagmus present. Lower limbs spastic, spastic paretic gait. Tendon-jerks increased. Plantar responses of Babinski type.

Urine: no pus or albumin; sugar present (0·5 per cent. in twenty-four hour specimen). On a previous admission to hospital a year earlier no glycosuria was present.

Blood sugar: (fasting) 0·103 per cent.

Wassermann reaction (serum) negative.

July 4: Spinal fluid: cells, 11/3. Protein (after Bisgaard): globulin, 1; albumin, 25. Wassermann reaction, negative.

July 19: Cells, 8/3. Protein: globulin, 1-2; albumin, 24.

July 15: Sugar administration test.

I.

10 a.m.		Morning urine, no sugar
10·15 ,,	Fasting blood-sugar 0·100 per cent.	
10·30 ,,	50 grm. glucose + 200 grm. water	
10·50 ,,	Blood-sugar 0·132 per cent.	
11·10 ,,	,, 0·155 ,,	
11·40 ,,	,, 0·123 ,,	
11·50 ,,		Urine, no sugar

July 17.

II.

9 a.m.	Fasting blood-sugar 0·098 per cent.	Morning urine, no sugar
9·5 ,,	50 grm. glucose + 300 grm. water	
9·25 ,,	Blood-sugar 0·139 per cent.	
9·50 ,,	,, 0·166 ,,	
10·30 ,,	,, 0·139 ,,	Urine, with sugar
10·45 ,,	,, 0·100 ,,	
11·30 ,,	,, 0·091 ,,	

Threshold . > 0·155 per cent.
< 0·166 ,,

This is a case with repeated vague periods of fever, after which a spastic paraparesis has developed and short periods of diplopia have occurred. Slight mental symptoms developed, and the spinal fluid was definitely pathological. Further, a glycosuria with a low threshold was found. The glycosuria seems to have developed during the same time as the disease of the nervous system.

The most likely diagnosis, chronic epidemic encephalitis, points towards lesions of the same part of the brain as in the previous case, and therefore also in this case the glycosuria has been looked upon as the result of a reduced sugar reabsorption in the tubules, which must be due to a disturbance of neuro-hypophyseal function.

Case 3.—Unmarried, smith. February 7, 1908.

Admitted at the Rigshospital, Department for Nervous Diseases, November 16, 1929. Discharged on January 14, 1930.

Diagnosis: Diabetes insipidus symptomatica: dystrophia adiposogenitalis; tuberculosis pulmonis.

Patient's father probably died from pneumonia. A sister of patient's father died from pulmonary tuberculosis and a cousin of the father had been operated upon for glandular tuberculosis.

Four years before his admission the patient had pneumonia with an exudate in his right pleura. Since then he has not been well. One year before his admission he complained of increasing thirst and passed much urine.

He has grown tired and feels ill and had difficulty in doing his work. Has lost in weight. He observed that his sexual potency and libido, which have previously been well developed, diminished. The growth of his beard is also less. He says that "he can sleep at any time." He hardly ever perspires. On a few occasions his sight has been dimmed for a short period.

On objective examination the following was found: Appearance younger than his age; no hairs in the axillæ, pubic hair scanty; testes atrophic, but otherwise no adiposo-genital or acromegalic symptoms. Neurological examination: bilateral Babinski phenomenon.

After a month's stay at the hospital the patient became febrile, an affection of the lungs with tubercle bacilli in the expectoration was found, and the patient was moved to a department for tuberculosis.

November 17: Urine contained no albumin, pus or sugar. Wassermann reaction (serum) negative.

November 19: X-ray examination of cranium and epiphyses showed nothing abnormal.

November 21: Spinal fluid: cells 188/3 (lymphocytes). Protein (after Bisgaard): globulin, 3—4; albumin, 21. Wassermann reaction, negative percentage quotient: 52. A-L-S-R.: 0·026 per cent.

November 23-26: Standard metabolism—86 per cent.

January 3: Blood-sugar test.

9·20 a.m.	..	100 grm. glucose, blood-sugar (fasting)	0·094 per cent.
9·30 „	..	0·5 mg. adrenalin (Medicinalco)	
10 „	..	Blood-sugar	0·251 „
10·30 „	..	„	0·286 „

Urine after experiment: no sugar.

During his stay the patient drank 5 to 8 litres of water and the amount of urine in twenty-four hours was 5 to 8 litres. Specific gravity, 1002-1005.

Subcutaneous injection of 1 c.c. pituitrin (P. D. & Co.) reduced the amount of urine and the consumption of water in twenty-four hours to about 2½ litres.

Subcutaneous injection of sol. phlorizini, ½ per cent., 1 c.c., did not cause glycosuria: the urine was examined for five hours after the injection.

Neither on a combined phlorizin + pituitrin (1 c.c. + 1 c.c.) injection was it possible to find glycosuria, although the diuresis was reduced and the patient was thirsty.

While in the two first patients it was supposed that the hypophyseal dysfunction caused a reduction in the reabsorption in the tubules, it must in this case be assumed that the reabsorption is increased, which also agrees with the clinical symptoms of hypophyseal defect. From the point of view of his glycosuria, this patient presents a perfect clinical "corresponding negative" to the other two patients.

It was not possible to cause excretion of sugar in the urine, though there was a high blood-sugar, by the injection of phlorizin. Not even when pituitrin was administered together with phlorizin, so that the urine was less diluted, was it possible to produce glycosuria.

According to the Cushney-Rehberg theory it is only possible to explain the effect of the phlorizin by a reduction of the power of reabsorption in the tubules; therefore, in the last patient we must assume that the power of reabsorption is so much increased that phlorizin is not able, as under normal circumstances, to reduce the power of reabsorption to such a degree that glycosuria arises.

On account of the pulmonary tuberculosis, which made it necessary to remove the patient to another department, I did not succeed in finishing the examinations I had planned, examinations which might have revealed interesting results. It was not determined whether the diabetes insipidus in question was of the hyper- or the hypo-chlorhydræmic type (Veill). Nor were the attempts at producing glycosuria finished, for instance a combination of phlorizin, hyperglycæmia and pituitrin might have been tried.

But, together with the already existing investigations, this case supplies a valuable supplement to the theory that in certain cases of cerebral glycosuria there is a connection between the function of the kidney tubules and the neuro-hypophyseal apparatus.

Even though these investigations of cerebrally-conditioned glycosurias do not form a foundation for a definite etiological or pathogenetic division of these conditions, the A-L-S-R threshold and filtrating determinations have made it possible to group these diseases more definitely when working clinically with glycosurias. By comparing this grouping with other clinical features, as the course of the disease, and with pathologico-anatomical investigations, it may be possible to determine more accurately their etiological and pathogenetic factors.

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THE RELATIONSHIP BETWEEN THE INTENSITY OF TONE-STIMULI AND THE SIZE OF THE RESULTING CONDITIONED REFLEXES.

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PREVIOUS reports from the physiological laboratories of Professor Pavlov in Leningrad have stated that the magnitude of a conditioned reflex is proportional to the strength of the stimulus which calls it out. This report presents the results obtained when that proposition is put to test with more suitable apparatus for producing and for controlling the relative intensity of tones than has been available in these laboratories in the past.

PROCEDURE.

In the experiments reported here, the usual technique was adopted for eliciting the conditioned reflexes. The dog was put in a chamber which was virtually sound-proof. The observer controlled the stimuli from outside and observed the animal through a periscope. The flow of saliva from the dog's cheek displaced water in a horizontal manometer. In these experiments the size of the conditioned reflexes is reported in scale-divisions on the manometer, five of which represent one drop of salivary secretion (0·05 c.c.). Detail of the method can be found elsewhere [7].

Since the aim was to get valid quantitative results, the experiments were always carried out at very nearly the same time of day, the same order of successive stimuli was followed throughout each series of measured observations, the time-intervals between stimuli were kept the same and the secretion in the intervals between stimuli was noted. Attention was also paid to spontaneous flow of saliva without a conditioned stimulus at the end of a period equal to the usual time-interval between stimuli ("time-reflex"). With one dog the interval-secretion and time-reflex often proved to be appreciable, and the results of a few experiments were discarded on that account. The interval-secretion had to be controlled from time to time by temporarily discontinuing experiments with the tones of different intensities, by feeding the dog a little before experiments, increasing the length of the intervals between stimuli, and introducing "negative stimuli" which were not followed by food ("differentiation"). The time-reflex could be eliminated for the purposes of these experiments by waiting seven, eight or nine minutes between all the usual stimuli which were given daily and which quickly led in this dog to time-reflexes at the end of those longer intervals; then, on those relatively few occasions when tone-stimuli were given and measured, such a stimulus would be begun five minutes after the preceding stimulus, at a time when there would be minimal interval-secretion and no time-reflex.

The tones which were used as stimuli were produced by a low-frequency oscillator (type 377-B), made by the General Radio Company of Cambridge, Mass., U.S.A., and an electromagnetic transmitter (No. 542 B.W.), made by the Western Electric Company of New York City.[1] A calibration for frequency of oscillation is at hand for the oscillator. The characteristics of the transmitter are unknown to us. The wave-form of the sounds produced has not been determined here, but previous work by one of us with the same oscillator and a similar transmitter in the United States showed sine waves for tones above about 250 vib./sec. The tones in the experiments in this report were arbitrarily taken at 1,000 vib./sec. and were kept at the same pitch throughout. They were, accordingly, probably pure tones, although no definite statement can be made to that effect. These tones could be varied in intensity from vibrations below the threshold of audibility to sounds which were moderately loud. No very loud tones could be produced by this arrangement of the apparatus.

The intensity of the tones is assumed to be proportional to the square of the current from the oscillator to the transmitter. Relative measures of output of the oscillator were made by shunting the current from the oscillator through a thermocouple connected with a sensitive millivoltmeter immediately on ending each stimulus. These instruments were made by Hartmann and Braun, of Frankfurt a/M. A calibration curve provided for this thermocouple-millivoltmeter gives readings in milliamperes, which then appear squared in the appended tables. This procedure for obtaining figures, representative of the relative intensity of the tone-stimuli, is considered justified, since the frequency of oscillation was kept constant and the resistance in the circuit remained the same for all measurements.

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[1] We are indebted to Mr. F. W. Bishop, of Rochester, N.Y., for procuring these instruments for us and for advising us as to their use.

The dogs which were used in these experiments were selected particularly with view to constancy of conditioned secretion from day to day. In addition, it is of course desirable to find in a dog fairly large salivary reflexes but small amounts of interval-secretion, and also it is important that conditioned reflexes to tones be easy to establish and to maintain without significant change over a considerable period of time. A dog which sleeps on the stand, a highly excitable or strongly inhibited type of animal, introduces useless complicating factors into a situation which is already complex. And so, preliminary inspection of several dogs, with their records of conditioned reflexes, reduced the available number to a very few animals at the start, and then actual trial with the tone-reflexes proved that conditioned reflexes were peculiarly hard to establish, or else were inconstant from day to day after being established in two of them. There remain for this report the protocols of only two dogs which could be carried satisfactorily through the series of experiments as planned.

RESULTS.

The first dog had previously been used in quantitative work with conditioned reflexes and had given large and constant daily salivary responses to all positive stimuli. Preliminary experiments with this dog then suggested that, when tone-stimuli were repeated on the same day, the size of successive reflexes would be affected by that of preceding reflexes to tone. Accordingly, during the first series in which careful measurements were consistently made, only one tone-stimulus, always in fourth place, was given during an experiment and, before another such experiment was run, there was at least one intervening day on which the dog worked with other conditioned stimuli but not with any tone. The duration of this series was from October 27, 1930, to January 24, 1931, during which only fourteen valid readings were made, although for the most part the dog routinely worked with other conditioned stimuli daily, six days out of seven. From time to time interval-secretion had to be reduced by the measures previously described. One period of excessive interval secretion came early in December and led to the rejection of data obtained on December 8, 11 and 13. On two other isolated occasions, November 5 and 13, the results were also discarded on account of appreciable interval secretion. All other experiments in which tone stimuli were used appear on Table I.

INTENSITY OF TONE-STIMULI AND RESULTING CONDITIONED REFLEXES.

Date	$\overline{MA}^2$	Tone-reflex	Percentage of total secretion	
November 3	0·16	3	1·0	
December 29	0·72	0	0	
January 7	1·4	27	10·2	Measured interval-secretion was 0
January 11	2·6	32	11·5	Measured interval-secretion was 0
December 26	3·4	24	11·1	
November 17	6·1	28	11·3	
October 27	7·3	43	15·1	
December 5	8·5	40	12·4	
January 4	15·5	53	?	
January 24	26·4	57	17·9	
January 17	31·8	58	16·2	
November 27	41·5	57	17·2	
November 29	41·9	58	19·5	
January 14	49·8	62	20·7	

ORDER OF STIMULI WITH TABULAR SUMMARY OF CONDITIONED REFLEXES TO STIMULI OTHER THAN TONE IN THIS SERIES OF EXPERIMENTS.

	Min.	Max.	Average	Standard deviation
	In scale-divisions on manometer			In drops of saliva
Metronome	71	107	90 4	2·016
Light	28	72	49·8	2·447
Bubbling	66	100	83·8	1·555
(Tone)	—	—	—	—
Metronome	48	92	67 9	2·406

Table I.—First series of experiments with first dog shows correlation between intensity of tone-stimuli expressed in terms of $\overline{MA}^2$ and size of resulting conditioned reflex when tones were given at random intensities and at infrequent intervals.

On Table I the data are arranged according to increasing strength of tone-stimulus expressed as $\overline{MA}^2$. Under the heading of "Tone-reflex" are the absolute numbers of scale-divisions of salivary secretion. It also seemed desirable to have some expression of the amount of salivary secretion which would take account of some daily changes in the magnitude of all the conditioned reflexes, for on some days all would be some ten scale divisions or so higher or lower than on others, and still the proportions of one to another would be closely maintained. And so, in the fourth column under "Percentage of total secretion" are the relative values of salivary secretion. The secretion brought out by the variable tone-stimulus is given there in terms of percentage of the sum of the rest of the salivary conditioned reflexes resulting from all the other stimuli which were constant in quality, intensity, order and timing on each day of experimentation. Also the minimal, maximal and average scale readings on the manometer, as well as the standard deviation of the size of the reflexes when measured in drops of salivary secretion (0·05 c.c.), are given for all these other conditioned reflexes in the order used in the experiment, so as to provide a standard of comparison of the daily reflex variability to stimuli of constant intensities.

Table I gives the results of tone stimuli at 1,000 vib./ secs., produced continuously for thirty seconds on each period of stimulation, spaced at intervals of at least two days between consecutive applications, and for the most part taken at different degrees of loudness from experiment to experiment quite at random. This dog shows that it is then possible to have a very close correlation between the intensity of the tone-stimuli and the magnitude of the conditioned reflex. Whether the absolute number of scale divisions of salivary outflow (column 3), or the percentage of each day's total reflex secretion (column 4) be selected makes but little difference in this series of readings. As inaudible vibrations increase in intensity and cross the threshold of audibility, there is in this dog an abrupt change from no secretion at all to twenty-four or more scale-divisions of saliva. As the tones become progressively louder, the corresponding increase in salivary reflex becomes less.

There were preliminary experiments with this first dog which suggested that the order or sequence of stimuli was important, especially when tones of similar or different intensities were produced at intervals of no longer than one day apart. Hence a short series of experiments was run with this in view on a second dog. This dog had a little more daily variation in the size of his conditioned reflexes, but had the distinct advantage of never having any interval-secretion nor time-reflex, nor restless habits on the stand during the period of these experiments.

INTENSITY OF TONE STIMULI AND RESULTING CONDITIONED REFLEXES.

Date	$\overline{\mathrm{MA}}^2$	Tone-reflex	Date	$\overline{\mathrm{MA}}^2$	Tone-reflex
November 17	5·90	6	November 29	42·51	60
November 18	10·24	20	November 30	47·89	46
November 20	9·12	6	December 1	46·24	26
November 21	7·24	24	December 2	6·10	37
November 22	7·02	19	December 5	5·62	43
November 23	5·57	22	December 8	24·70	35
November 24	5·90	32	December 11	2·40	14
November 25	44 36	5	December 13	32·25	67
November 27	18·06	25	December 15	2·37	10
November 28	41·09	32			

ORDER OF STIMULI, WITH TABULAR SUMMARY OF CONDITIONED REFLEXES TO STIMULI OTHER THAN TONE IN THIS SERIES OF EXPERIMENTS.

	Min.	Max.	Average	Standard deviation
	In scale-divisions on manometer			In drops of saliva
Bell	0	60	44·1	2 496
Metronome	11	84	58·0	3·274
Light	6	51	21·6	2·178
(Tone)	—	—	—	—
Metronome	35	78	53 7	2·427

Table II.—Series of experiments with second dog shows wide variation in conditioned reflexes but no correlation between intensity of tone-stimulus and size of the reflex when several tones given daily at low intensities were followed by several at high, and vice versa.

Table II gives the results with the second dog of tone-stimuli at 1,000 vib./secs., produced continuously for thirty seconds during each period of stimulation, beginning with the twenty-seventh trial, arranged in chronological order, with successive stimuli coming daily for a couple of weeks and then at intervals of two or three days for a couple of weeks longer. The notation and arrangement is similar to that on Table I. This dog showed, during the first couple of days, changes in the magnitude of the conditioned reflex which ran parallel to the intensity of the tone stimulus. From then on, random choice of tones of varying loudness was stopped. A tone of low intensity but well above the threshold of hearing ($\overline{MA}^2$ = 9·12 on November 20) was followed by a series of four tones of slightly lower intensity. The salivary reflex increased in size. Then for six days relatively loud tones were given as stimuli. The resulting salivary reflexes failed to jump at once to correspondingly high readings, and only on one occasion (tone reflex = 60 on November 29) was there a rise to the size that was expected in view of the intensity of the tone-stimulus. Then a change of the stimulus back to one of low intensity ($\overline{MA}^2$ = 6·10 on December 2) failed to reduce proportionately the size of the salivary reflex. Finally, random choice of different intensities of tones at intervals of at least two days apart gave for a few days some semblance of reflexes of corresponding size but no close correlation. The experiments had to be discontinued at this point.

Since these experiments on the second dog were of short duration and in themselves not conclusive, another series on a similar plan was run at a later date on the first dog. This time a distinct change was made in the organization of the work. Two preliminary experiments were carried out with the tone-stimulus at low intensity, in order to accustom the dog to a change of schedule. Then, beginning on February 4, for fourteen consecutive days with a gap of one day, two tone-stimuli were given each day, in third and fifth places respectively. For the first five days the intensity of the tones was low; the dial readings on the oscillator were 2 throughout, and when expressed in terms of $\overline{MA}^2$, they varied between 5·29 and 5·43, with an average of 5·34 $\overline{MA}^2$. Then for six days the tones were relatively loud, dial readings on the oscillator were about 18; the $\overline{MA}^2$ varied between

47·1 and 49·7, with an average of 48·7. And then for three days the intensity was again low with the dial readings at 2.

On Table III the results are arranged chronologically. The intensity of the tones is given here in dial readings on the oscillator. The size of the reflex appears as scale-readings on the manometer. Throughout this series, the data show that the size of the conditioned reflexes remained very nearly the same in spite of marked variation in intensity of stimuli. In fact, the appended figures which summarize all the reflexes in this series prove that the set of conditioned reflexes to varying tone-stimuli in fifth place on the schedule were practically as constant as those to metronome, just as constant as those to bubbling, and distinctly more uniform than those to light. The metronome, bubbling of air through water and electric light were of course stimuli of constant intensity. Thus, in this second series of experiments with the first dog a correlation between intensity of tone-stimulus and size of resulting conditioned reflex is conspicuous by its absence.

INTENSITY OF TONE-STIMULI AND RESULTING CONDITIONED REFLEXES.

Date	Dial reading on oscillator	Tone-reflex in 3rd place	Tone-reflex in 5th place
February 4	2	76	88
February 5	2	71	76
February 6	2	77	76
February 7	2	69	74
February 8	2	92	67
February 9	18	63	58
February 10	18	71	68
February 12	18	81	83
February 13	18	78	71
February 14	18	80	77
February 15	18	71	67
February 16	2	90	75
February 17	2	83	71
February 18	2	58	70

ORDER OF STIMULI, WITH TABULAR SUMMARY OF CONDITIONED REFLEXES TO ALL STIMULI IN THIS SERIES OF EXPERIMENTS.

	Min.	Max.	Average	Standard deviation
	In scale-divisions on manometer			In drops of saliva
Metronome	89	121	102·1	1·492
Light	47	90	68·6	2·684
Tone	58	92	74·9	1·559
Bubbling	77	102	92·6	1·498
Tone	58	88	72·9	1·498

Table III.—Second series of experiments with first dog. Shows very constant conditioned reflexes to tone-stimuli of widely different intensities when the latter were given twice daily and in groups at the same intensity before change to another.

Discussion.

Quantitative studies on the perception of differences in the intensity of sensory stimulation have long since been made on human subjects. Such investigations have usually been directed at the sensory organ involved, although the data were provided by one's ability to discriminate increments of stimulation, which is of course a function of the cortical cells in the brain. A stimulus may be given, and then measured increments in intensity of stimulation may be added, and the subject's ability to appreciate the differences be compared with the physical changes in the stimulus. When carried out through a range of different initial intensities, such data formed the basis for Weber's law (1846) and Fechner's law (1860), which have been applied to sensation in general, and for König's formula (1903) specifically for vision. These laws were expressed in slightly different mathematical terms, but in all of them the perception stood in an exponential relation to the intensity of the stimulus. The expansion of the physiology of the senses along these lines and criticisms of the validity of such " laws " lie outside the scope of this discussion. But recently, Macdonald and Allen [5] have applied this method to the " sense of audition." They used a Stern tone-variator, blown by air from a constant pressure tank, on which weights could be placed by a lever so as to give abrupt increases in intensity of the sound, keeping the frequency of vibration constant. The person would listen for two seconds to a sound, and then the increment which produced a just perceptible sudden increase in intensity would be determined by repeated trial. A series of such measurements was made throughout the range of the tone-variator and the results were treated mathematically. They found that the relation of the reciprocal of the increment of intensity to the logarithm of the intensity of the stimulus was a constant.

After developing a different method with a highly original technic, Professor Pavlov and his co-workers have shown that conditioned reflexes give quantitative responses to various stimuli of different intensities. In their work the rôle of the cortex usually occupied the centre of attention. However, the data collected here in this report are offered as a presentation of the integrated responses of the whole animal to tone-stimuli without particular focus of attention on the function of the cortex. On several occasions, studies of the conditioned reflexes have been made in Professor Pavlov's laboratory with various stimuli of different intensities. For example, Kasherininova [3] reported that salivary reflex responses increased with the strength of tactile stimuli, and Orbeli [6] showed that visual conditioned reflexes increased with greater intensity of illumination. Working with sounds, Tichimirov [9] tried to establish differentiation of loud and soft sounds and observed during this work that the stronger stimuli gave a bigger reflex effect than the softer. Zeliony [10] used an organ, a whistle and a pitch-pipe, controlled the physiological effect of intensity by placing the dog at different distances from the source of the sound (outside a chamber), and also reported larger reflexes as the result of stronger stimuli. Also, with complex stimuli made up of more than one auditory component, he observed the resulting reflexes when the components were given separately and together. He assessed the intensity of sounds with his own ear. After he had established a conditioned reflex to two different tones of equal loudness, each component was tested singly and gave reflex responses of equal size. If the compound stimulus contained one loud and one soft tone, the louder tone gave a larger reflex than the softer one when tested separately, Moreover, a whole cord produced a greater reflex response than any single component. Work by Rikman [8] and a study along the same general lines by Kupalov and Gantt [4] dealt with the summation of various "strong" and "weak" stimuli. The latter investigators used different types of stimuli, including tones of varying intensity produced by a Galton's whistle and by a telephone receiver. They drew the conclusions that "separate employment of the components of a complex conditioned stimulus is a reliable method of determining their relative strengths. In a complex of two stimuli, the main effect is produced by the stronger stimulus, and this may even inhibit the weaker component. A strong light and cold are more potent stimuli than a very faint sound. The size of the conditioned reflex reaction depends upon the strength of the stimulus, that is, upon the energy transmitted to the cerebral cortex." Andréev [1] produced tones with an oscillator and transmitter, and controlled their intensity with a rheostat. He used five settings on the rheostat, giving different degrees of loudness of the tone from a very soft to a loud tone. From previous experiments he found that 2,600 vib./sec. provided an optimum pitch for discrimination of intensity with dogs, which is higher than the optimum for man, and most of his work was done at that frequency of vibration. His protocols show fairly consistent results from which he draws the conclusion that conditioned reflexes to tones vary in direct proportion with the intensity of the stimulus.

Feshchenko [11] used strokes of a pendulum against a wooden board as source of sound-stimuli. Variation in the angle of deviation gave different intensities of sound. The mean value of salivary conditioned reflexes showed a linear relationship to intensities of the sounds. However, the deviation of the readings from the mean value was very large. He arrived at the equation

$$I = \overrightarrow{Sr^{2}}\,\frac{\alpha}{2}A$$

where I = intensity of stimulus.
Sr = size of reflex.
α = angle of deviation of pendulum.
A = constant.

In this present paper, the data which appear on Table I were collected by the method of conditioned reflexes without differentiation. Tone-stimuli of different intensities were given without any conception that the dog would consciously discriminate increments of change. Furthermore, the intervals of over a day between stimuli were almost prohibitive of any accurate discrimination of that sort. Finally, the fact that salivary reflexes and not speech served as the indicators of the effect of the stimuli favoured the elimination of subjective factors in this work. And so there are significant differences in approach between the psycho-physical study made by Macdonald and Allen, mentioned

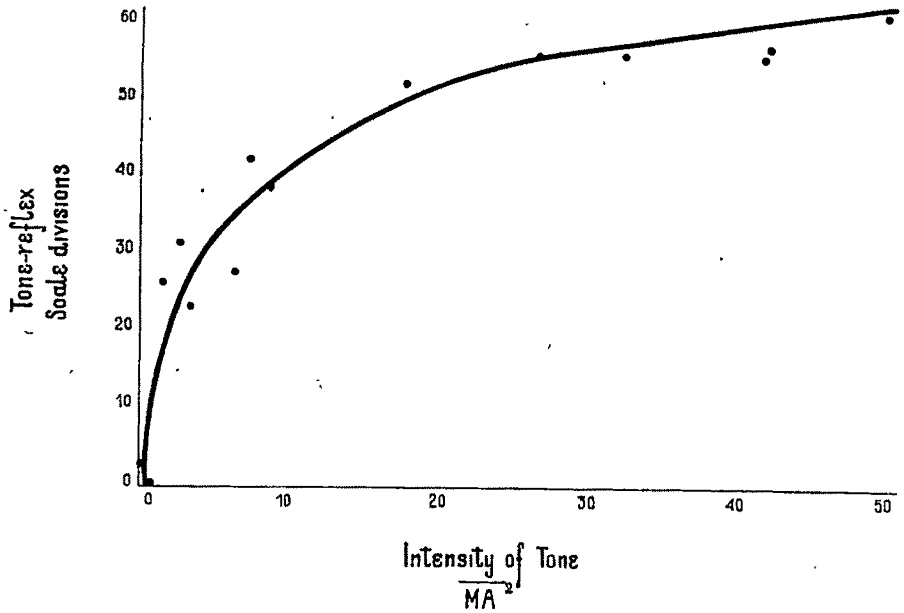

FIG. 1.—First series of experiments with the first dog. Points on plot represent experimental data. The curve satisfies the equation : y = log$_e$ x + C, where a is about 11 and C about 13 in this case.

above, and the physiologico-physical data reported here. The readings of the conditioned reflexes in our work are not reproduced with the accuracy that is obtained in physical laboratories, but they do present enough order to allow a plot to be made and a representative curve to be drawn. This appears on fig. 1. There are only fourteen readings in the series, but the length of the experiment and the close similarity of successive reflexes which followed stimuli of proportional intensities over that period of four months indicate that the results were not a matter of mere chance. On fig. 1 the intensities of stimuli, expressed relatively in $\overline{\text{MA}}^2$, appear as abscissæ and scale-divisions of salivary conditioned reflexes as ordinates. An equation[1] can be assigned to the curve:—

$$y = a \log_e x + C.$$

where a is about 13 and C is about 11 in this particular case. In finding that equation, only the curve itself was satisfied and no further attempt was made to obtain a formula with the best possible match for each single point that was determined experimentally. The differences in principle underlying the experiments of Macdonald and Allen with our own necessitate that the data and plots appear dissimilar. In both cases, however, on graphs constructed with intensity of stimulus on a common logarithmic scale, the experimental points did *not* lie on a straight line. Since the Canadian investigators plotted logarithms of intensity of stimulus against increments of intensity, the conclusion was drawn that their data did not substantiate Weber's law. With our data, where the logarithms of intensity of stimulus were plotted against salivary reflexes without attention to threshold increments, no such direct deduction was permissible. The second form of graph presented by Macdonald and Allen is a plot with *log I* as abscissæ and $\frac{1}{\Delta I}$ as ordinates. That curve provides their formula:—

$$\frac{1}{\Delta I} = -k^2 \log I + C$$

Two adjoining straight lines appear, running down to the right, and thus giving the negative sign to k^2. Each linear part of their curve, which shows a single abrupt change in its slope, satisfies their equation. Closer comparison between these different formulas and curves does not seem warranted. The results of conditioned reflexes with the dog reported here are merely not inconsistent with the experiments carried out with threshold increments of intensity on human subjects by Macdonald and Allen in Winnipeg.

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[1] We are indebted to Maria Ivanovna Petrashen of the Department of Mathematics in the University of Leningrad for determining this equation from our data and for advice about other mathematical aspects of our work.

Thus, with one dog and with one series of experiments on that dog, the size of the conditioned reflexes to tone-stimuli varied in an orderly way with the intensity of the sound. But, with a few other dogs and with this same dog at a later date and under a different schedule of work, no such relations existed. The reason for one set of consistent variations of reflexes with the intensity of stimulus, and for the other series of experiments with total absence of such variations on the same dog, is not clear to us. Naturally, in attempting to determine any physiologico-physical relationship of this sort, many extraneous influences should be controlled. From this work it would seem that the frequency and number of times that similar stimuli are given is of great importance. A change in those two factors alone was the only obvious alteration made in the schedule of the first dog reported here. When relatively few tone-stimuli of different intensities taken at random were given to this dog, with at least one intervening free day, the size of the conditioned reflexes varied with the intensity of the sound as shown on Table I and fig. 1. When groups of tone-stimuli, first of low intensity and then of high and again of low, were given with two stimuli from a group in each daily experiment, the conditioned reflexes remained consistently constant in magnitude regardless of the intensity of the sound, as shown on Table III. Failure of the conditioned reflexes to vary with the intensity of the stimulus in the second series of experiments can hardly be attributed just to the fact that this series was second, and therefore represented merely a process of the dog being more accustomed to the procedure and its significance, because the same tendency was noted in unsystematic work with the same dog before the first series was begun, and also because a similar failure of correlation under a somewhat similar schedule appeared in the initial series of systematic experiments reported here with our second dog, summarized on Table II.

Many other factors doubtless enter into this problem as added complications. Thus, for want of more exact terminology, the "type" or "constitution" of the animal may be significant. For example, another dog proved quick to give conditioned reflexes to the sound of a metronome and of air bubbling through water, but in a trial lasting about six months reflexes to a tone from the oscillator were at the start slow in becoming established and then always remained very unreliable in magnitude. With still another dog the conditioned reflex to tone was very difficult to establish, while reflexes to certain other sounds proved relatively easy. In contrast, the two dogs reported in this paper immediately acquired and maintained reliable conditioned reflexes to tones from the oscillator.

The type of stimulus itself—a continuous tone which may be considered "pure" (sine wave)—deserves consideration. These tone-stimuli sometimes required relatively long application before conditioned reflexes would result; they were often followed by salivary reflexes of inconstant amount and tended to fluctuate, or even drop out entirely after unusual situations or slight trauma (e.g., after exposure to Roentgen rays of a part of the head not directly over the temporal lobes); they always provided conditioned reflexes of smaller size than certain noises or impure tones (e.g., bubbling, bell, metronome, which of course also adds the quality of being interrupted).

The real significance of these differences in response to tones opens up fields of inquiry unsettled by this present report; the difference in physiological effect of continuous and intermittent sounds; the ability of the dog to discriminate quality of sounds (wave-form), or even to discriminate noises (aperiodic) from tones (periodic vibrations); the question of smaller or more sharply focal "centres" in the cortex for "pure" sounds of specific pitch, allowing perhaps more ready fatigue than larger areas which consist of more cells and connections; and also, the possibility of other biological explanations, involving for example the difference in significance to the animal of various types of sound, and hence in physiological development and adaptation to them by the animal. Noises in nature can well have much meaning for the dog and musical tones practically none. Thus a difference in anatomical as well as in physiological development between dogs and men, a phylogenetic result dependent upon the rôle of musical sounds in their lives, might arise and provide a distinct difference in their ability to respond to tones. Börnstein [2] goes so far as to state that on this account the auditory cortex of mammals functions "not for the hearing of tones but for the hearing of noises."

Other features which we have considered as having a possible influence on this kind of work include the rapidity of learning with subsequent changes in salivary responses, the orientation reaction of the animal to the stimulus, the order of stimuli with reference to the use of "strong" and "weak" types of stimulation, and also variations of the particular dog at hand for optimal frequency of vibrations and for optimal duration of stimuli and for optimal time intervals between stimuli. The slightly variable position of the head with respect to the source of sound might provide a minor source of difficulty.

There are enough incompletely controlled complicating factors in these experiments to account for the lack of exact reproducibility of the data. But in spite of imperfection in the results, enough consistency prevails to lead to the beliefs that conditioned reflexes to auditory stimuli are governed by definite principles, that no single principle will cover completely even the interdependence of intensity of stimulus and size of resulting salivary reflex. but that one, and probably the most fundamental, of those principles is the tendency for the magnitude of the conditioned reflex to increase with the intensity of the tone-stimulus in a relationship that is probably exponential, similar to that shown on fig. 1 of this paper.

SUMMARY.

(1) Tone-stimuli of varying intensity, but the same pitch from below, the threshold of audibility to moderately loud sounds, were produced with an oscillator and transmitter, and the resulting conditioned reflexes were measured.

(2) In one series of experiments lasting four months with one dog tone-stimuli were varied in intensities taken at random and an interval of at least one day without tones was always given. A close correlation existed between the intensity of the tones and the size of the resulting conditioned reflexes. The relationship was exponential and a formula was found for a curve drawn to represent the experimental data.

(3) No such correlation existed in another series of experiments with the same dog and in an initial set of similar experiments with a second dog. In these experiments the tone-stimuli were kept at the same intensity for several days, then abruptly changed to another widely different intensity for several days more, and then back to the original intensity. Moreover, these stimuli were given daily or twice a day.

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A SEARCH FOR TROPHIC INFLUENCE OF POSTERIOR SPINAL ROOTS ON SKELETAL MUSCLE, WITH A NOTE ON THE NERVE FIBRES FOUND IN THE PROXIMAL STUMPS OF THE ROOTS AFTER EXCISION OF THE ROOT GANGLIA.

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THAT the posterior spinal roots should exert a certain beneficent influence on the skeletal muscle which they supply is to be expected by virtue of the sensory fibres contained in them and coming from the muscle. For on the proprioceptive sensory impulses arising in a muscle the reflex activity of the muscle largely depends. And a supply of pain fibres affords protection against injury to muscle, as to any other structure.

Recently, however, it has been suggested by Kuré and his collaborators (1925-30), that the posterior roots contain efferent nerve fibres which control the trophic state of skeletal muscle in a more direct manner. According to these authors (Kuré, Saegusa, *et al.*, 1930), about 40 per cent. of the fibres constituting a normal posterior root have their cells of origin in the spinal cord and are distributed in the periphery, probably with synapse in the root ganglia. Destruction of this innervation results, in the experimental animal, in dystrophic and atrophic changes in the skeletal muscle. In man, lesion of this fibre system is supposed to produce the syndrome of progressive muscular dystrophy. According to the present thesis of this group of workers, sympathetic innervation of skeletal muscle aids and abets the posterior root "parasympathetic" innervation in its trophic functions. In earlier publications the sympathetic innervation bore the task alone. Experimental and clinical evidence is presented in support of these ideas.

The author has dealt in a previous publication (1931A) with the question of sympathetic trophic control of muscle. No evidence could be found for it. Bearing on the theory of dorsal root "parasympathetic" control, the extensive posterior rhizotomies performed on man by neurosurgeons the world over, have not brought on dystrophic sequelæ in muscle. But autopsy or biopsy specimens from such cases of rhizotomy must be examined if the question is to be finally settled. It is to be hoped that the material and data will soon be available. For the experimental animal, however, the problem is open to quick solution.

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[1] Fellow of the Henry Strong Denison Medical Foundation, under whose auspices this work was started.

MATERIAL; METHODS.

Four adult cats were used for the experiments. Under ether anæsthesia, the spinal canal was opened in the lower cervical—upper thoracic region. The posterior rootlets of a segment were picked up in the cuff of dura mater which envelops them, and cut about two millimetres proximal to the ganglion. After carefully separating dorsal from ventral roots, the dorsal root ganglia were excised. In one animal the stellate ganglion was also removed, after exposure in the proximal end of the first intercostal space.

The animals were kept four months, six months and a year. During this time they were examined every four weeks—pain sensibility, as reaction to prick; deep sensibility, as mewing in response to deep pressure; proprioceptive sense, by the presence or absence of shortening and lengthening reactions. The range of motor activity was thoroughly tested and the bulk of the muscles estimated in comparison with the normal. Lastly, the trophic condition of skin and hair was watched. On the expiration of the allotted time, the cats were killed with ether, and two litres of physiological salt solution, followed by one litre of the fixative (20 per cent. formalin neutralized by saturation with magnesium carbonate), were perfused through the vascular system.

After six months or more in the fixative, specimens for histological study were removed and put through a modified Bielschowsky staining technique. The interosseous muscles of the fore-foot were selected as being the muscles most exclusively supplied by the spinal roots attacked. The entire fifth interosseous muscle was cut in serial sections longitudinally at 15 μ. Serial cross sections at 10 μ were made from the middle of the belly of the fourth interosseous muscle. In all cases normal and experimental specimens were treated alike.

OBSERVATIONS.

Dorsal root ganglionectomy.—Three cats survived this operation four, six and twelve months respectively. In the first animal, removal of the dorsal root ganglia of C7, C8, and T1, produced anæsthesia of ulnar distribution, complete loss of prick pain over the fifth digit, partial loss over the fourth, and in a strip extending along the ulnar border of the fore-arm to the elbow. In the other two animals, excision of the ganglia from C 6 to T 2 resulted in girdle anæsthesia extending from the mid-dorsal to the mid-ventral line and including, in the second animal, the entire arm except for a strip narrowing down to encircle the first toe pad; in the third animal only the point of the shoulder.

The sensory loss, as briefly outlined, increased or decreased slightly from time to time depending on the animal's alertness, but there was no consistent regression. Although the de-afferented fore-limb was little employed, every movement normally possible, even to extrusion of the claws and spreading of the toes, could be elicited. Overaction then characterized the movements. In no case was there appreciable loss of bulk in any group of measles, or contracture. The only changes affecting skin or hair were obviously the result of abnormal posture; the hair on the dorsum of the paw was worn thin; the skin of the paw pad was not worn off. However, injuries in the region of partial denervation healed very indolently.

When the killed and fixed material was available, measurement substantiated the estimate. The fore-arm, skinned and disarticulated at the elbow, and the fifth interosseous muscles were weighed. Table I presents the data of experimental and normal specimens from the series of cats. The degree of de-afferentation of the specimen was, of course, various. In S VII b (and S VIII a) muscles of ulnar innervation would be those chiefly affected by the lesion. But since it was impossible to elicit any proprioceptive reflexes whatever from the fore-arm in S VII d, every muscle here was devoid of dorsal root innervation. And S VII c approached this state. Yet even in S VII d, deprived totally

TABLE I.

Animal	Operation	Survival Time in days	Wt. of fore-arm in grm.		Wt. of M. Int. V. in mg.		Av. size 100 fibres	
			N	O	N	O	N	O
							μ	μ
S VII b	D.R.G. C. 7 to T. 1	112	37	35	360	330	27	26
S VII c	D.R.G. C. 6 to T. 2	182	55	54	250	240	25	29
S VII d	D.R.G. C. 6 to T. 2	364	49	48	240	240	31	27
Av.	D.R.G.	215	47	46	280	270	28	27
S VIII a	D.R.G. C. 7 to T. 1 St. Gang.	112	38	38	350	370	28	29

of dorsal root innervation for one year, the loss of weight in the partially denervated specimens was so trifling as to be less than the experimental error. Furthermore it can be said in passing, that in the fixed specimens no wasting was noted in the more proximally situated muscle groups, the upper arm and back muscles of the segments affected by the lesions.

Gross examination of living and fixed material having failed to disclose any trophic disturbance in muscle attendant on removal of dorsal root and root ganglion innervation, study of microscopic preparations was resorted to. In the serial longitudinal Bielschowsky preparations of the interosseous muscle, no distinction could be drawn between operated and normal specimens save in one particular—the loss of the sensory endings on the spindles. In no other respect was the lesion evidenced. The innervation of the extrafusal fibres was intact, and nerve fibres and motor end-plates appeared quite normal. The muscle fibres of the de-afferented specimens likewise showed no disturbance. They were neither larger nor smaller than in the control specimens, nor were hypertrophic fibres as figured by Kuré, Hatano, *et al.* (1925), encountered. The cross and longitudinal striations were clear cut, and there was no fragmentation along either of these planes. There were no signs of fatty or hyaline degeneration. And lastly, the amount of connective tissue in the operated specimens did not exceed the normal. Figs. 1 and 2 present, for comparison, the region of motor nerve distribution of fascicles from normal muscle and from the muscle deprived of dorsal root innervation for one year.

Yet the evidence of inspection seemed not quite sufficient. Therefore, with the aid of a micrometer eye-piece and mechanical stage, the diameters of 100 muscle fibres were measured in the cross sections taken from the middle of the belly of the fourth interosseus muscle. The fibres were chosen at random, ten in each of ten sections lying 100 μ apart. Table I gives the average diameter of the 100 fibres for each of the specimens examined. Although from animal to animal there were slight differences between experimental and normal specimens, these differences were not consistent. Figs. 3 and 4 show, in cross section, muscle fascicles from each fore-limb of the animal surviving operation one year.

We now possess all the pertinent data: condition of the muscle during an average of seven months of post-operative life; weight of gross fixed specimens; microscopic appearance of the muscle fibres; measurements of the diameter of six hundred fibres. Yet this mass of observations gives no indication that depriving the cat's skeletal muscle of all innervation derived from dorsal roots and root ganglia, both afferent and possible parasympathetic efferent, for a period of time up to a year, occasions any gross or microscopic disturbance in the muscle. Atrophy and dystrophy were equally absent. In the case of atrophy this is indeed surprising, because the use of a limb is so much curtailed by deafferentation that a certain loss from disuse was expected. Perhaps, however, the gross overaction which characterized the use of the muscles when they were brought into play, served to compensate the general lack of exercise of the limb.

Dorsal root and sympathetic ganglionectomy.—Although removal of afferent innervation and of the hypothetical dorsal root "parasympathetic innervation from muscle proved to be without effect on the trophic condition of the muscle, it seemed possible that the addition of sympathetic denervation to this lesion might prove the potent combination bringing on the dystrophic and atrophic changes. In one cat, therefore, the stellate ganglion was removed, together with the dorsal root ganglia C7 to T1. This animal was allowed to survive sixteen weeks.

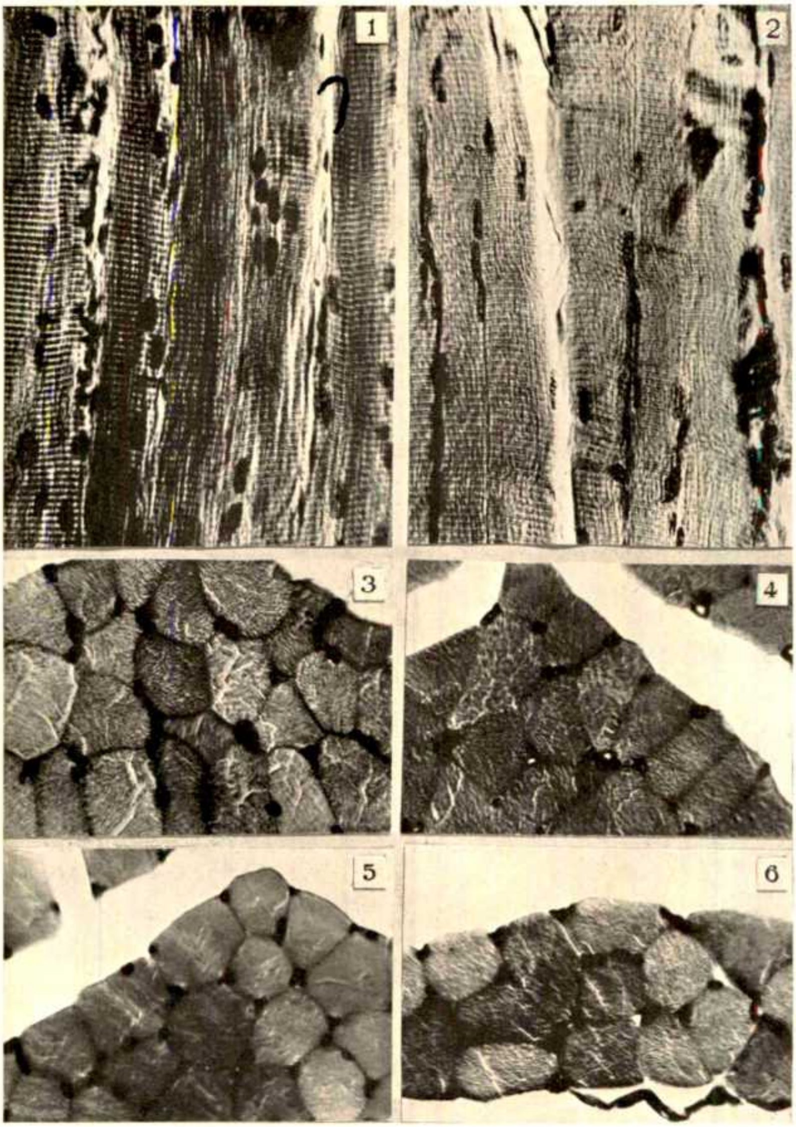
During the four months of life, again, no trophic disorders were noted nor any wasting of muscle bulk. When the gross fixed specimens were weighed (Table I, S VIII a) the weights of the two fore-limbs were equal, whereas the fifth interosseous muscle from the side of operation was slightly heavier than its control. The average diameter of 100 fibres of the partially denervated material was also slightly greater than the average of the control. On close study of the microscopic sections, no morphological characteristic served to distinguish the extrafusal muscle fibres from the side of the lesion from the normal muscle fibres (figs. 5 and 6). And again, no large fibres such as appear in progressive muscular dystrophy were to be found. Apparently, then, sympathetic, parasympathetic (?) and afferent denervation is no more effective than the latter two alone, in producing dystrophy or atrophy of skeletal muscle. In view of the completely negative results of this one trial it did not seem worth while to extend the experiment over a larger series or a longer time. For the trophic function under investigation can not be subject to variation from animal to animal in the mechanism of its maintenance. It is a basic physiological state.

A note on nerve fibres present in the proximal posterior roots after excision of the root ganglia.—From the fixed specimens of three of the cats of the series (S VII b, S VII d, S VIII a), the spinal segments C 7, C 8 and T 1, were removed, together with the attached spinal roots, and including the site of lesion. The T 1 specimens were put through modifications of Marchi technique for formalin material. The C8 segments were prepared according to Bielschowsky technique for nerve fibres. The C 7 segments were stained by the Weigert-Pal method for myelin sheaths. The specimens were cut serially at 15 μ, the material from each animal in one of the three planes—transverse, sagittal horizontal—referred to the spinal cord as axis. In each instance, again, the normal control was given the same treatment as the experimental specimen.

The Bielschowsky preparations proved most illuminating. The nerve fibres of roots and cord were excellently stained. On examining sections from the side of the lesion, nerve fibres were to be found in the proximal stumps of the posterior roots of all the material, varying only in number. They were most numerous in the preparations from the cat which survived operation one year, S VII d. Here, the numbers of the fibres rendered an attempt at counting them a tremendous task, and in view of their obvious origin quite pointless—but in each of the intradural rootlets of a segment they were present in hundreds (fig. 7). The fibres present in all the material were fine, 2 to 3 μ or less, rarely more. They tended to be grouped in bundles, especially in the more distal portions of the roots and in the scar tissue. Often, half a dozen fibres appeared to occupy an hypertrophied sheath of Schwann—a Büngner's band. Study of the Weigert-Pal preparations showed that the majority of the fibres present four months after operation were unmyelinated. Here and there were fine deposits of myelin, an occasional fibre thinly coated. After one year, however, many, if not most of the fibres were thinly and evenly medullated.

Traced peripherally, most of the fibres in the dorsal root clearly took origin from the ventral root. At the site of removal of the dorsal root ganglia there were unmistakable signs of regeneration, spools and whorls of nerve fibres and large axones ravelling into many smaller axones (fig. 8). By this last process the characteristic bundles of fine fibres were formed. Quite obviously, then, we are dealing with the condition long ago studied by Lugaro (1906)—invasion of the sensory paths of the proximal dorsal root by motor fibres from the ventral root.

Numbers of the fibres and fibre bundles of the posterior roots finally entered the dorsal horn of the cord. Their manner of entry was, however, peculiar. Present in hundreds in each intradural rootlet, they



Untouched contact prints of photomicrographs, taken with 4 mm. apochromatic objective, × 10 compens ocular. Figures on the left are of normal muscle, those on the right are of muscle from the side of operation.

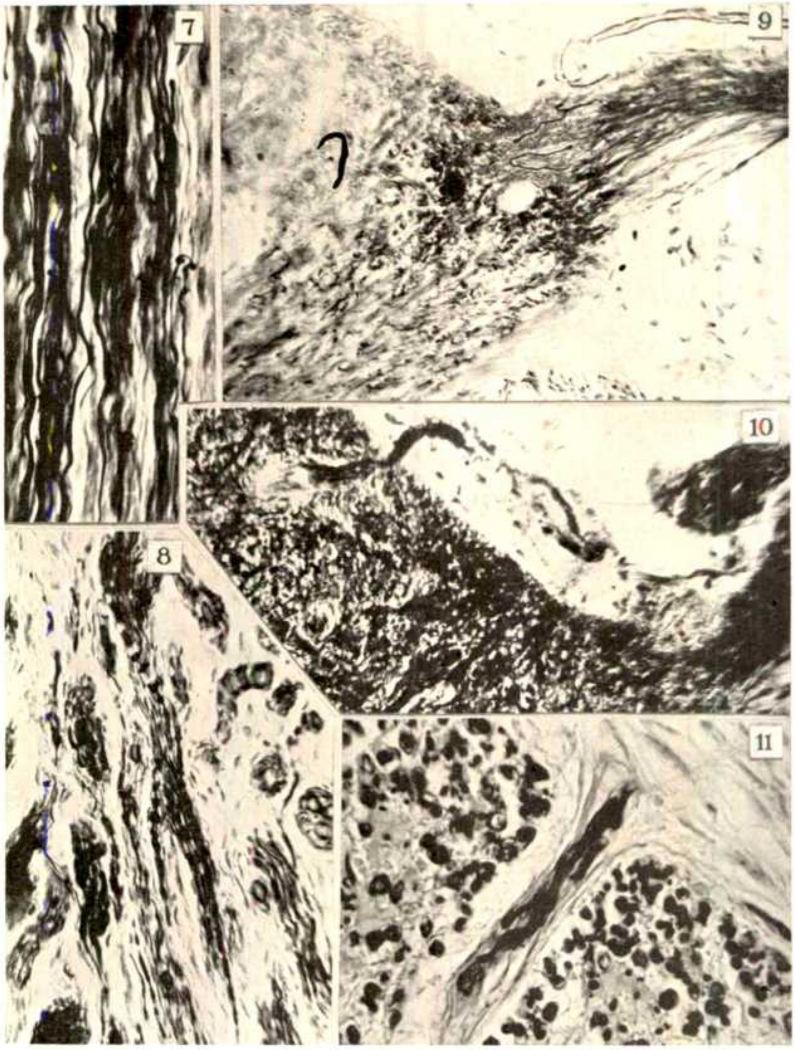
FIGS. 1 and 2.—Cat S VII d; fifth interosseous muscle taken one year after excision of dorsal root ganglia of C 6 to T 2.

FIGS. 3 and 4.—Same; fourth interosseous muscle.

FIGS. 5 and 6.—Cat S VIIIa; fourth interosseous muscle, taken four months after excision of the dorsal root ganglia of C 7 to T 1, and of the stellate ganglion.

To illustrate paper by Sarah S. Tower.

PLATE II.



Photomicrographs of the spinal cord and roots of Cat S VII d, killed one year after excision of the dorsal root ganglia of C 6 to T 2.

FIG. 7.—Showing nerve fibres in one of the intradural rootlets of the eighth cervical segment. Bielschowsky preparation; 4 mm. apochromatic objective, × 10 compens ocular.

FIG. 8.—Showing the cicatrix from removal of the dorsal root ganglion of C 8. Nerve fibres growing from the superficial layer of the ventral root into the dorsal root. Regeneration figures are plentiful. Bielschowsky preparation; 8 mm. apochromatic objective, × 10 compens ocular.

FIG. 9.—Showing the point of entry of the posterior rootlet of fig. 7 into the spinal cord, and the manner of ending of the two nerve fibres penetrating farthest. Bielschowsky preparation; 8 mm. apochromatic objective, × 10 compens ocular; retouched.

FIG. 10.—Showing a bundle of nerve fibres penetrating the dorsal horn in pial connective tissue; posterior rootlet at right. Bielschowsky preparation; 8 mm. apochromatic objective, × 10 compens ocular.

FIG. 11.—Showing myelinated nerve fibres penetrating the spinal cord along a blood-vessel. Weigert-Pal preparation; 4 mm. apochromatic objective, × 10 compens ocular.

To illustrate paper by Sarah S. Tower.

occupied largely, if not entirely, the vacated sheaths of Schwann. Directed along these tracts, they entered the root portion of the spinal cord, and immediately neuroglia took over the support of the fibres (about half a millimeter outside the cord) their course became tortuous and short. Fig. 9 shows the two nerve fibres of a rootlet which penetrate the neuroglia farthest. The one turned back on itself, the other divided, and each of the fibres terminated in a small "growing" knob. A little deeper, the intrinsic fibre bundles of the cord can be seen quite intact. It is doubtful if any nerve fibres succeeded in penetrating through the sclerosed posterior root region into the deeper normal parts of the spinal cord. Figs. 9, 10 and 11 show, however, the manner in which fibres did make entry into the depths of the cord. Leaving the posterior root where the latter acquires neuroglia, nerve fibres coursed singly or in bundles through the pia-arachnoid, and these fibres penetrated the posterior horn through the adventitia of blood-vessels. Some few fibres even ascended in the pia, to penetrate the posterior funiculus or mid-dorsal line along the connective tissue septa. Within the degenerated posterior horn and column region the perivascular spaces were much enlarged. In these, bundles containing a few or several dozen nerve fibres were everywhere to be seen. No such groups of nerve fibres could be found in the normal material. If vasomotor nerve fibres accompany the blood-vessels of the cord, they are sparse and inconspicuous. No confusion on this score is possible, for in the experimental material of the cat surviving operation one year (S VII d) the fibres penetrating the cord from the pia in the eighth cervical segment alone would number some hundreds.

Within the spinal cord the fibres quickly lost their myelin sheaths (fig. 11). But their axis cylinders could be traced in the Bielschowsky preparations to great depths. In the preparations from the cat surviving operation one year (S VII d) some were followed very nearly to the central grey. The unusually strong argentophile reaction of regenerating fibres, originally described by Cajal, made it feasible to trace the fibres. Bundle formation and varicosity characterized them, and their common association with the blood-vessels. The fibres increased rapidly in number within the cord, by ravelling or by simple division. But some of the bundles, or single fibres from the bundles, appeared to leave the side of the blood-vessels to penetrate the adjacent tracts or the neuropile of the dorsal horn. Indeed, isolated and seemingly naked fibres unquestionably traced long and complicated paths among the neuroglia of the depleted dorsal horn and column. Their course then was, to all appearances, aimless. They were not oriented with the tracts, nor were they directed toward cells, either nerve cells or the hypertrophied neuroglia. Thus the invading nerve fibres, which had been unable to make headway against the dense, almost a-cellular neuroglial tissue of the degenerated posterior roots, were fairly well distributed in the interior of the cord. Their manner of ending was, however, always typically that of regenerating axones—a knob or loop. Nothing suggestive of a functioning nerve ending was seen.

It was not always possible to decide whether or not those regenerating axis cylinders were accompanied by neurolemma. In their course in the roots and pia and in the large perivascular spaces of the cord, the fibres were generally sheathed by cells resembling Schwann cells. But the fibres which departed from the perivascular spaces to follow intricate paths in the neuropile and tracts of the cord seemed to be naked.

No single remaining dorsal root ganglion cell was encountered in any of the preparations. Such a source, then, for any of the fibres present in the posterior root need not be considered. And since the fibre content of the roots of cat S VIIIa did not differ noticeably from that of S VIIb, and in the former animal the stellate ganglion had been removed together with the posterior root ganglia, the sympathetic could have contributed no appreciable portion of the fibres seen. Quite obviously, the ventral root was the major source of the fibres invading the vacated posterior root stumps. However, there was evidence that a few other nerve fibres of the vicinity, fibres in the connective tissue or from the adjacent traumatized muscles, were assisting in the process. The ventral root fibres involved in this regeneration were chiefly the superficial layer adjacent to the cicatrix. The bulk of the fibres of a ventral root continued into the spinal nerve without deflection or modification. Although by using care the anterior and posterior roots can be separated so that no motor defect results, yet nevertheless the ventral root is so intimately applied to the dorsal root ganglion, in the cervical region of the cat, that the surface layer of the fibres would always, even in the best operation, be injured. These few injured fibres were the stock which by repeated division and by the process of ravelling fill the posterior roots vacated by excising the dorsal root ganglia.

These observations confirm, then, the opinion of Sherrington (1894, 1897) and many others (most recently, Nevin, 1930), that the nerve fibres found in the proximal stumps of severed posterior roots are regenerating fibres. Although they give credence to the figure offered by Kuré and Saégusa (1931) (40 per cent. of the normal fibre content), and confirm their description of the fibres as fine and finely myelinated, the belief of these authors as to the origin of the fibres—that they are efferent fibres proper to the posterior roots, remaining when the 60 per cent of afferent fibres degenerate—is not confirmed. Unfortunately, these Japanese workers prepared the posterior roots and spinal cords by different techniques. They studied the posterior roots in cross section, detached from the cord. Hence they could not have established the emergence of the fibres from the cord by examining the transition zone between them. The fibres present in such great numbers in the posterior roots disappear rapidly in this region. They neither enter nor emerge from the cord, except a small fraction which utilize the perivascular connective tissues as route of entry, and curiously enough this small fraction which gained access to the cord in such a roundabout way, once inside, increased tremendously in numbers and coursed with seeming ease among the cells and fibres of the central nervous system.

DISCUSSION.

This history of physiology contains a series of attacks on the Bell-Magendie concept of the function of posterior roots as exclusively sensory. The phenomenon of antidromic vasodilatation, so thoroughly examined by Bayliss (1901), has not been brought into discredit, but the well-planned experiments of many investigators have, as yet, failed to explain it fully, or to incorporate it as a mechanism of the intact animal. Attempts to assign to the posterior roots or ganglia, a rôle in the maintenance of tone in skeletal muscle, other than their exceedingly important share in the sensory path of the proprioceptive reflex arc, have not fared so well. The data presented in this paper now fail to provide any support for the most recent suggestion that the posterior roots and ganglia, with or without assistance from the sympathetic nervous system, are concerned in maintaining the normal trophic state of skeletal muscle, and that destruction of this innervation results in dystrophic and atrophic changes in the muscle. Muscle deprived of innervation of dorsal root origin for a year, or of dorsal root and sympathetic origin for four months, failed to show any trace of atrophy or dystrophy. Such partially denervated muscle was, indeed, quite indistinguishable from normal muscle by any morphological characteristic except the absence of sensory nerve endings.

These results conform with our concepts of the innervation of the fibre of skeletal muscle. No efferent connection of posterior roots with skeletal muscle has been described. In preparations made by the author (1931 B) of cat's muscle in which the dorsal root component of innervation had been isolated by degenerative section of the ventral and sympathetic components, nerve fibres were to be found ending in the spindles, in the connective tissue, and occasionally running along blood-vessels, but none was ever seen ending hypolemmally or epilemmally on an ordinary muscle fibre. Indeed, it is not at all certain that there are efferent fibres in the posterior roots of the higher mammals. The preparations examined in the present study show clearly that the nerve fibres found in great numbers in the proximal stump of a severed posterior root have grown in from the ventral roots. And although it cannot be denied from the data in hand that there were among these regenerating fibres a few that were truly efferent, emerging from the cord with the posterior root, no fibres suspected of this origin were encountered. In lower vertebrates, fish, amphibia and birds (Kappers, 1920), efferent fibres most certainly exist in the posterior roots.

On the other hand, even should it be proven that the posterior roots contain nerve fibres structurally efferent, it would still be necessary to prove that these were functionally efferent also. They might function as sensory fibres equally with the remainder of the root fibres. The fibres of the mesencephalic root of fifth cranial nerve are a case in point. Furthermore, their peripheral distribution would remain to be determined before their connection with skeletal muscle could be accepted. For Kuntz and Farnsworth (1928) have described fibres passing from posterior roots to the grey rami of the sympathetic system, although to be sure only in regions of the cord giving rise also to sympathetic efferents. But in any case, even should a small component of efferent nerve fibres be demonstrated in the posterior roots, the evidence here presented seems conclusive that their function is not essential to maintaining the normal trophic state of skeletal muscle.

SUMMARY.

The posterior root ganglion supply of the muscles of one fore-limb was removed in four cats, and in one of these the stellate ganglion also. After four, six or twelve months the animals were killed, gross specimens weighed, and histological preparations of interosseous muscles and spinal cord segments made.

During life, no atrophic or dystrophic changes were noted in the fore-limbs affected by the lesions. Likewise, weighing fixed specimens brought out no significant difference between experimental and control material. Furthermore, the microscopic preparations yielded no morphological evidence of atrophy or dystrophy. And on measurement the diameter of 400 muscle fibres from the side of operation and of 400 normal fibres averaged the same.

Study of the spinal roots and cords showed numbers of fine nerve fibres in the posterior roots. Some of these fibres penetrated the spinal cord along the blood-vessels, but none, probably, through the root zone proper. They were most numerous in the longest surviving specimen. Many of the fibres could be directly traced from the ventral roots.

The conclusion is reached that the posterior roots play no essential rôle, either alone or in association with sympathetic innervation, in maintaining the normal trophic state of skeletal muscle.

" Trophic state " is a phrase which is loosely used throughout neurological literature. When a substantive is employed, a verb is assumed. Hence, perhaps, the search for " trophic control." Yet, does the trophic state of a tissue express anything other than the capacity of the tissue to function ? And in this case, indeed, is the concept of " trophic state " at all necessary ? Previously, the author has shown (1931A) that the sympathetic nervous system plays no rôle in maintaining the trophic state of skeletal muscle. Now it is apparent that the dorsal roots and ganglia likewise exercise even less influence of this nature than was expected by virtue of the sensory fibres coming from the muscle, which the roots mediate. The trophic state of skeletal muscle seems, indeed, to be solely dependent on motor innervation. (The effects or ventral root lesion on skeletal muscle need not be recapitulated). In other words, the function of muscle and its physical integrity go hand in hand. Trophic state ceases, then, to be a physiological entity, a phenomenon with a mechanism peculiar to itself. Like tonic state, trophic state becomes, in this light, one aspect of the function of the neuromotor unit.

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NOTICES OF RECENT PUBLICATIONS.*

Neue Deutsche Chirurgie. Heraus gegeben von H. KUTTNER in Breslau. 48 Band. Spezielle Chirurgie der Gehirnkrankheiten. Redigiert von Professor FEDOR KRAUSE. 3 Band. 1ster Bd. S. 743. Stuttgart: Ferdinand Enke. Price Rm. 96.

Each of the eleven sections into which this volume is divided is a monograph, the subjects thus comprised being the inflammations, suppurations, hæmorrhages, softenings, and some of the vascular tumours affecting the brain and meninges.

The work begins with an excellent article by Guleke (Jena), whose opening pages discuss the anatomy and physiology of the meninges and cerebrospinal fluid. He insists that considerable quantities of the lumbar fluid are absorbed by the lymphatics of the spinal nerves via their arachnoid sheaths. In an attractively general statement of the aims of treatment in meningitis arising from extradural suppuration, he lays stress on the protective character of meningeal adhesions, and thus he considers that treatment should aim at localization.

There is an orthodox chapter on cerebral abscess from the hand of Willich (Jena), though we cannot agree with his commendation of encephalography in the diagnosis of this condition as, in our opinion, it must be dangerous. In treatment he rightly insists on the use of a small dural opening for exploration and drainage so as to obviate, if possible, meningeal spread. There follows a long and again orthodox exposition of the intracranial complications of aural and nasal infections by Bruhl (Berlin), but nowhere have we found in long accounts of the diagnostic and prognostic importance of the cerebrospinal fluid changes in suppurative conditions, a reference to diminution of chlorides. The remainder of the book deals with vascular lesions (Smidt, Bremen).

Intracranial aneurysms are discussed and the effects of their treatment by carotid compression and ligation. Very high percentages (42 per cent. and 25 per cent. in different classes of case) are mentioned as the incidence of paralytic sequelæ to ligation, far higher than we believe to obtain, and probably falsified by the small number of cases quoted.

There is a short reference to congenital venous tumours, and to varices, but no doubt the hæmagiomas will receive attention in the coming volumes.

Throughout the book the clinical and neurological aspects receive the same care that is devoted to the pathological and operative expositions.

Études Neurologiques. Quatrième Serié. Par G. Gullain et Th. Alajouanine. Pp. 358. Paris: Masson et Cie. 1930. Price 65 francs.

The three preceding members of this series of clinical and pathological studies have already been noticed in this Journal. Like its predecessors, it is a collection of papers that for the most part have appeared already in medical periodicals. The reader will find that this volume follows the plan and maintains the standards set by the authors in earlier collections.

Handbuch der biologischen Methoden. Abt. v. Methoden zum Studium der Funktionen der einzelnen Organe des tierische Organismus. Teil 7, Heft. 7. Price Rm. 8.

The present section of this handbook contains three articles: On the Registering of Vocal Curves by means of the Kathodophone and the String Galvanometer, by R. Roseman; The Investigation of Vibration Sense, by D. Katz; and New Methods of Investigating Temperature Sense, by H. Hahn. These articles, which are primarily concerned with methods of quantitative testing, are highly technical and do not lend themselves to brief abstract. Their study is of importance to workers engaged upon research in the subjects with which they deal.

Perspektiven der Seelenheilkunde. von Arthur Kronfeld. Leipzig: George Thieme. 1930. S. 384. Price Rm. 25.00.

This large book is for the specialist. Kronfeld is no easy writer, and so thorough and detailed an attempt to seize the psychic essence of schizophrenia cannot be read through at a few sittings or summarized in a few lines; even psychiatrists, unfamiliar with philosophical psychology, will find it hard reading.

The author's grasp of the relevant literature is prodigious, and he covers the whole ground systematically according to a method based on the teachings of Jaspers and the Heidelberg school, but with considerable personal variation. It cannot be said that much emerges that is new; but the present position with regard to schizophrenia is clarified and the available methods of research examined as to the possibility of their leading to further knowledge. It is, however, only with the psychological and philosophical approach to the problems that the author is concerned, and as to this he closes with an expression of resignation, for he sees inevitable limits, already reached.

Soziale Krankheit und Soziale Gesundung. von Viktor v. Weizsacker. Berlin: Springer. 1930. Pp. 52. Price Rm. 2.80.

Professor von Weizsäcker, whose valuable work on the physiology of perception and in neurology generally is well known, has given his attention to the great social problem of the millions of people who receive State support in the form of pensions and sick pay. Anyone who has had to examine these patients, particularly in the capacity of expert, is aware how closely medical and social considerations are intertwined, and how difficult may be the deciding of the question whether a man is fit to work and whether responsible work is the only form of treatment that will save him from chronic invalidism. Professor von Weizsäcker's method of observing such patients, of determining their fitness, and of treating them so that they may become fit to work, is original and has bearings on related problems. All who are confronted with this issue would do well to read the small book, in which there is much wisdom both of theory and practice.

The Psychology of Intelligence and Will. By H. G. Wyatt. London: Kegan Paul, Trench, Trübner and Co. 1930. Pp. 273. Price 12s. 6d.

This is a bold and close-knit attack on many of the most assured and widely held assumptions of current psychology. It arose out of the disappointment that the author felt when for educational needs he sought a helpful theory of intelligence and volition, but discovered that "there is much measuring of intelligence, but few attempts to fathom it, and will is apt to be disposed of by treating it as something else."

The book is divided into three parts: in the first various theories about intelligence are examined, including those of Thorndike, Spearman, and the Gestalt school; in the second part the relation between intelligence and instinct is taken up, and the stability and constancy of instinctive ends is contrasted with the changing progressive quality of intelligent ends, the assertion of which as dominant is man's unique achievement. In the last part the will is considered, not so much as a part of experience but as a factor in conduct. It is concluded that volition is a "faculty" which enables man to master impulse, that is, to act in opposition to a strong desire and in observance of a principle or pursuance of an end recognized by intelligence as the most desirable in the circumstances.

So careful an examination of the problem as may be found in this book and so drastic a knocking away of wobbly pillars in the accepted psychological edifice cannot be dismissed lightly; it is, however, to be deplored that the author has paid little heed to medical psychologists whose systems are more nearly related to ordinary experience than those of the experimentalists, and no heed at all to the large and influential school, headed by Freud, for whom "psychical determinism" is axiomatic.

The Concentric Method in the Diagnosis of Psychoneurotics. By M. Laignel-Lavastine. London: Kegan Paul, Trench, Trübner and Co. 1931. Pp. 217. Price 10s. 6d.

Professor Laignel-Lavastine's interest in mysticism and the religious experience, as well as his work on the relations of the sympathetic nervous system and the internal secretions to mental disorder, find expression in this collection of informal clinical lectures. The easy familiar style, peculiar to this mode of presentation, and the author's cultivated mind, showing itself in a wide range of allusion and illustration, make the book a pleasant and smooth one to read, but it is discursive, in many ways superficial, and there is a good deal of repetition. The habit of mind which it expresses is not familiar to us in England, though it may do more justice to the present state of psychiatry than precise systematic study or more complicated conceptual schemes. Every method of approach is to be valued, and the case for the analytical and logical has not yet been established beyond question in the field of mental disorders. And so Professor Laignel-Lavastine's comparison between psychoneurosis and religious experience, on which he builds, and his definite pronouncements about endocrine and other humoral disorders in these people, deserve consideration.

On matters of detail there is a good deal contrary to accepted practice nowadays, e.g., "There is one form of travel which eliminates hotels, motor-cars and railways, and which is of enormous benefit to psychoneurotics—I mean sea-voyages. They are especially suitable for the depressed, on whom the sea air has a very beneficial effect"; the section on psychotherapy is stoutly and assertively old-fashioned, and the general tenor of the book amazingly conservative and at times uncritical. The concentric method, from which the work takes its title, is another name for that consideration of all the relevant facts which is now the rule among all good psychiatrists. The translation, an anonymous one, is occasionally faulty and obscure.

Die Neurosen des Lebenskampfes. von W. CIMBAL. Berlin: Urban und Schwarzenberg. 1931. S. 356. Price Rm. 12.50.

This work is the continuation of the author's earlier book on the neuroses of children. He considers that it is the function of the physician not only to relieve the neurotic of his infirmities but to sustain him with advice in the conflicts of daily life. The modifiable factors in these conflicts are set forth, to the end that rules of life may be found for the individual which will avert failure and consequent illness. In so far as the work is a study of the difficulties, as between social forces and the individual, in Western European society, and of the relative capacity of people to lead satisfactory lives in such circumstances, it is excellent, but the tendency to make of the physician a counsellor and prop for the weakest, ill or well, is to ignore economic and biological considerations of an obvious kind. One must also take exception to the author's proposal that his book should on occasion be put in the hands of the patient, for whose sake he has eschewed all unfamiliar words. The practice of giving patients works of this kind is fruitful of mischief, though the temptation to take such an apparently easy and time-saving short cut may be hard to resist. In the actual description and classification of the problems of daily life, family relationships, &c., the book contains useful and interesting material.

Die Organischen, einschliesslich der Exogenen, Reaktionstypen. Von Professor H. KRISCH. 1930. S. 146. Berlin: Karger.

Bonhoeffer's doctrine of exogenous reaction-types has been the basis of all recent teaching with regard to "organic" mental disorders. But Krisch and some others have, in the last ten years, given their attention to the less acute and gross cerebral traumata. From the standpoint of "empirical dualism," the author here investigates afresh the problem of what psychic symptoms are co-ordinated with organic stimuli working on the brain. He finds the concept of intensity of stimuli, as developed by him in this connection in earlier writings, to be one of great heuristic value. Disturbance of consciousness he regards as the fundamental organic symptom, and its intensity as the measure of the cerebral damage.

After an introductory chapter on the development of the doctrine of symptom-complexes, and on general concepts such as are expressed by the terms ætiology, constitution, localization, symptom and syndrome, he passes to a careful clinical account of the organic types of reaction which may be met with in various conditions, including the so-called endogenous disorders; this forms the main body of the work. A chapter on disturbance of individual functions, as seen in bewilderment, confusion, flight of ideas, lack of initiative and disordered memory, with a brief discussion of guiding principles, concludes the work, which is a notable contribution, neither definitive nor claiming to be, but free from the weak assumptions and indifferent neurology sometimes conspicuous in books of the kind.

Influenza dell' Educazione Sugli Anomali Originarii. Da JACOB AISENSCITAT. Napoli: R. Stabilimento Tipografico Francesco Giannini and Figli. Pp. 536, con 59 illustrazioni. 1930. Price L. 150.00.

This bulky work contains much valuable and interesting material bearing on the education of children with congenital defects. In the first part the defective child is considered as to intelligence, sense-organs and affectivity; waifs and strays and children of criminals are also described. The causes of anomalies are next considered. Heredity in all its aspects receives the fullest consideration; the history of genetics, the various theories, the present status and problems are the subject of ten chapters; sections on neuropathic and psychopathic heredity, consanguinity, criminal heredity (in five chapters), the influence of syphilis, alcohol, tuberculosis and general distress, with a final two chapters on criminal women, make up the remainder of the first part. The second part, of nearly a hundred pages, is concerned with the various forms of education, not merely scholastic, the influence of education on animals and its evolution in the different human races, followed by a detailed account of the writer's own researches carried out at institutions in Naples and Pompeii and on a training ship, to ascertain how far inherited defects can be modified by training. His conclusions are encouraging and should be read in detail in the original.

The Sexual Reform Congress. Edited by NORMAN HAIRE. London: Kegan Paul, Trench, Trübner and Co. 1930. Pp. 670. Price 25s.

The Proceedings of the Third Congress, held in London in September, 1929, are contained in this book. The papers are of very unequal value, some of them enthusiastic to the point of ranting, and headlong. One would have preferred more knowledge and less zeal. The prevalent uncertainty about sexual matters, especially sexual ethics, and the extremes of opinion in this regard, become very evident as one reads. The less polemical and fervid papers, such as reports on social experiments, censorship, contraception, sterility, etc., are of interest, though far from conclusive.

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EDITOR.

JUNE, 1931.

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BRAIN.

PART 2, VOL. 54.

OBSERVATIONS ON THE TREATMENT OF EPENDYMAL GLIOMAS OF THE SPINAL CORD.

BY HUGH CAIRNS, F.R.C.S.,[1]
AND
GEORGE RIDDOCH, M.D.

It is a commonplace that the spinal cord must be treated with the greatest respect at operation. Interference with it during removal of an extramedullary tumour, by injudicious or rough manipulation, is apt to leave the patient more paralysed than he was before operation, and this risk is greatly increased when attempts are made to remove a tumour from within the spinal cord itself. Removal of tumours from the cervical or upper thoracic spinal cord has at times been followed by respiratory failure or by fatal hyperthermia. It was doubtless for this reason that Elsberg and Beer [1] introduced the "extrusion method" of treatment of intramedullary tumours. By this method at the first operation the tumour is exposed by an incision through the posterior columns, a week later the wound of operation is reopened and as much of the tumour as has meanwhile extruded itself through the incision in the spinal cord is removed. In this way the surgeon aims at removal of tumour tissue with minimum injury to the spinal cord itself. More recently it has been suggested that no attempt should be made to remove intramedullary tumours, but that instead they should be treated by X-rays, surgical measures being restricted to decompressive laminectomy [11].

The object of this paper is to show that there are certain intramedullary gliomas that can be completely removed without serious permanent injury to the spinal cord.

Cerebral gliomas vary greatly in structure, rate of growth and invasive powers, and the same variations are found in gliomas of the spinal cord. Some spinal gliomas grow rapidly, are richly supplied with blood-vessels and have no sharp line of demarcation from the surrounding nervous tissue. Tumours of this type do not lend themselves to surgical removal. But there are others which are quite circumscribed and of slow growth. Two such cases, both of them ependymal gliomas, have come under our care during the past two years, and in each it was possible to remove the tumour, apparently completely, with benefit to the patient. We propose to report these cases in full, because they illustrate many details of the surgical treatment and after-care of patients with intramedullary tumours. The case records show errors in treatment which might be avoided in future. And above all they illustrate the slow but continuous recovery of function of the spinal cord after a tumour has been dissected from its interior. Recognition of the need for long and patient after-treatment is in our opinion of considerable importance in these cases.

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[1] Working under a grant from the Rockefeller Foundation.

REPORT OF CASES.

Case 1. *Intramedullary ependymal glioma of cervical and thoracic spinal cord* (C.4—Th.3). Complete removal by two-stage operation. Great improvement.

History.—Mrs. S., aged 29, referred by Sir Ashley Mackintosh, was first seen on May 5, 1929, complaining of pain in the neck and gradually increasing weakness of all four limbs. She had always suffered from coldness of the extremities and for some years she had had slight pain in the left shoulder when tired. Otherwise she had enjoyed good health until January, 1928, when she began to have pain in the vagina after, and sometimes before, menstruation. This symptom was not severe and had disappeared six months before she came under observation. However, in March, 1928, fourteen months before admission, she began to have disturbances in her limbs, first sensory and then motor. The initial symptom was an intermittent numbness and "wooden feeling" in her right foot, which became worse after she had played tennis. Within a month she began to have numbness and tingling of the ulnar three fingers of the right hand, and later this spread to the index finger. Weakness came on in her lower limbs in June, 1928, at first only as a lack of springiness and an inability to run well. At the same time she found that she could not "do things" with her right hand when it was cold. By August, 1928, there was stiffness of both lower limbs which wore off as the day went on.

These symptoms, though slight, were enough to make her seek medical advice before her impending marriage. She was examined in September, 1928, by an expert neurologist, and as no signs of organic disease were said to have been found she got married. Soon after this her left knee at times began to give way and she occasionally had difficulty in going down stairs; also when driving her car she found that her feet were apt to slip from the controls. Her disability was not severe, even though there was now also numbness of the left foot, and in January, 1929, she could still walk three miles without becoming tired. In the following month, however, her right lower limb became weak and she was so unsteady that she fell down several times. The tiredness and stiffness of her lower limbs increased, and the symptoms were much worse at the menstrual periods. In March, 1929, six weeks before admission she was no longer able to walk and began to have painful flexor spasms of the lower limbs. At this time also her right hand became so weak that she could not wind up a clock, and tingling sensations began to occur in the tips of the ulnar three fingers of her left hand.

In addition to the disturbances in her limbs, she had suffered for twelve months before admission from pain in the back of the neck, from about the fourth cervical to the second thoracic spines, which was always eased by walking. This pain was not increased by coughing or straining, but sneezing was occasionally followed by a sensation of numbness down her back and lower limbs. During the same period she had had, when walking quickly, an occasional girdle sensation around the waist at the level of the umbilicus. Three weeks before admission a lumbar puncture was done and eight hours later this girdle sensation became so intense that she felt she was being cut in two, and at the same time became collapsed, and suffered from extreme stiffness of her lower limbs and inability to flex her head. These symptoms did not entirely disappear for nine days. During her illness the patient had had occasional headaches and once had vomited. For nine months before admission she had been constipated and had had some difficulty and urgency of micturition, with incontinence on one occasion.

Examination.—The patient had numerous freckles on her face; and on her left upper limb, above the external epicondyle of the humerus there was a hairy mole (1·5 cm. × 0·5 cm.). She was intelligent and co-operative. The optic discs appeared normal. The right pupil was slightly smaller than the left and it reacted poorly to light but well on convergence. There was slight ptosis of the right upper lid and enophthalmos of the right eye. An area of doubtful cutaneous analgesia was found on each side of the face (fig. 1).

There was moderate weakness and wasting, without dystonia, of the small muscles of both hands, especially the right, and to a less extent of the other muscles of the upper limbs, excepting those of the shoulders. All the muscles of the abdominal wall were weak and moderate spastic paresis was present in both lower limbs, more marked on the right side. The tendon jerks of both upper limbs were diminished, more so on the left side. The abdominal reflexes were absent. The knee-jerks were slightly increased and the ankle-jerks normal. The plantar reflexes were extensor and each was accompanied by flexion of the corresponding limb and extension of the opposite limb. Flexor spasms of the lower limbs occurred at times.

The areas of sensory loss are shown in fig. 1. There was complete loss of sensibility to cotton wool and pin-prick below the second thoracic dermatomere,

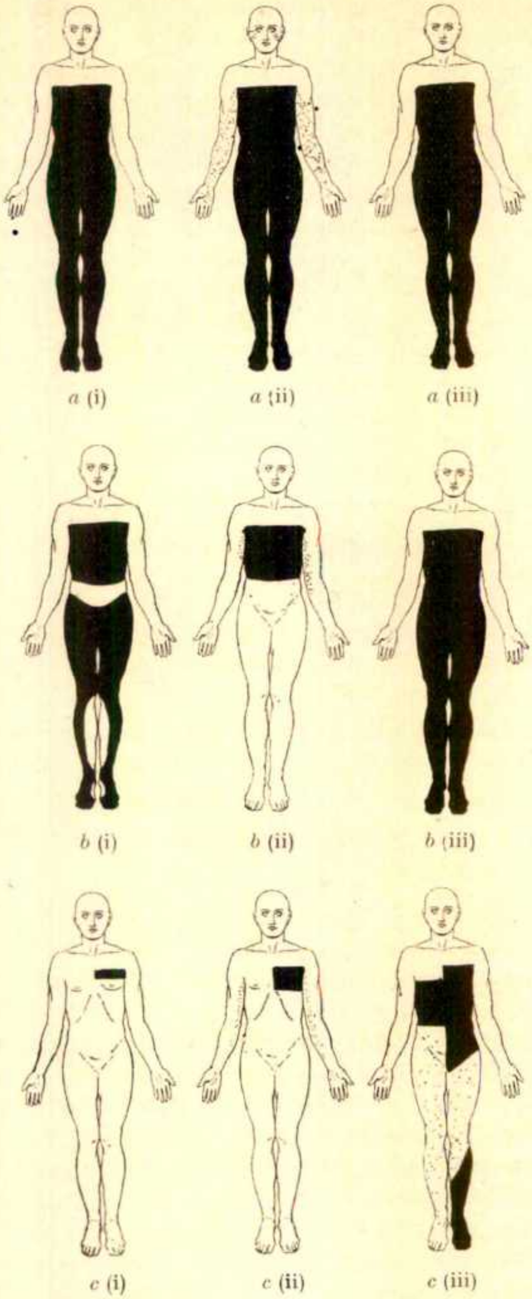

FIG. 1, *a*, *b*, *c*.—*Case* 1. Sensory changes before and after operation. (i) Cutaneous anæsthesia. (ii) Cutaneous analgesia. (iii) Loss of recognition of written numbers (Zahlenschreiben). (*a*, Before operation; *b*, 16 days after operation; *c*, 677 days after operation.)

except for some sparing of the sacral areas.[1] Over the same area vibration sense was lost and there was no recognition of numbers written on the skin (Zahlenschreiben). Postural sensibility was completely lost in the toes, ankles and knees. In the upper limbs sensibility to light touch was preserved, but there was relative cutaneous analgesia and thermo-anæsthesia up to the upper limit of the fifth cervical segmental distribution, slightly higher on the left than on the right side. Postural sensibility and tactile discrimination were normal in the hands and in all the fingers. No areas of cutaneous tenderness could be detected.

There was tenderness of the seventh cervical spine and to a less extent of the adjacent spines. X-rays showed a small cervical rib on each side. The toe-nails were brittle and the patient herself had noticed this during the period of illness. Lumbar puncture revealed a scanty amount of straw-coloured fluid at a resting pressure of 20 mm. of cerebrospinal fluid. No rise of pressure followed jugular compression. There were three cells per c.mm. and the protein content was much increased.

Diagnosis.—There was clear evidence of a lesion extending from at least the fourth cervical to the first thoracic segments. The upper limit was indicated by the boundary of sensory change and the lower by the wasting of the small muscles of the hand, as well as by the sensory dissociation on the upper limbs as compared with the complete sensory loss at the level of the second ribs. The relative absence of pain, the character of the sensory loss, and the sensory and motor indications of the longitudinal extent of the lesion suggested that it was intramedullary. At the same time the occurrence of a girdle sensation of the tenth thoracic level raised the possibility that there might be a double lesion.

First operation.—May 8, 1929. Ether anæsthesia. Five laminæ, from the fourth cervical to first thoracic inclusive, were removed. On opening the dura the presenting spinal cord was seen to be uniformly distended to an extreme degree, and it did not pulsate. The posterior columns were unusually wide and the lower end of the cervical enlargement was slightly yellow in colour. In the middle of the cervical enlargement there was a small area of bluish discoloration which suggested an underlying cyst. However, nothing but a little blood could be obtained by puncture and aspiration of the spinal cord at this point. As there was no pulsation of the cord or flow of cerebrospinal fluid the incision was prolonged upwards by removal of the third cervical lamina, whereupon cerebrospinal fluid began to escape. The diagnosis of an extensive intramedullary tumour was confirmed, and it was felt that it would not be right to attempt to remove the tumour without further consultation with the husband, himself a medical practitioner. The incision was accordingly closed in layers, except that the dura had to be left open.

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[1] Six weeks before the patient came under our care Sir Ashley Mackintosh had found that sensibility to light touch was preserved over most parts of the lower limbs and trunk, though all other forms of sensation were lost up to a level corresponding to the second thoracic segment.

Post-operative course.—For the first twenty-four hours after operation there was tachycardia (pulse rate up to 170), and micturition was frequent. A tiny blister developed on the right middle finger, probably from the application of a hot-water bottle immediately after operation. The right-sided cervical sympathetic palsy became rather more evident than it had been before operation. No other additional disturbance of spinal function was observed. There was, indeed, slight improvement in sensibility in the sacral and lower lumbar segmental areas, and the patient herself felt that her lower limbs were less

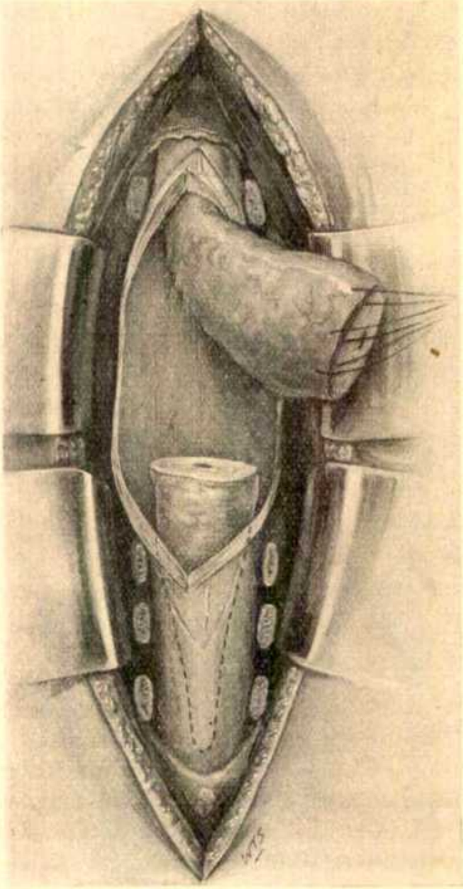

FIG. 2.—*Case* 1. Removal of tumour from the interior of the spinal cord. The tumour has been divided and the upper portion is being removed with the aid of traction sutures. The dotted line indicates the extent of the lower portion of the tumour.

heavy and that she could move them more freely. The flexor spasms of her lower limbs were less painful. This sensory improvement was considered as evidence against a second tumour in the lower part of the cord. At the upper limits of sensory loss light touch was now appreciated on the right side as low as the sixth thoracic segmental area: but on the left side the level was unchanged. Mr. Wilfrid Trotter kindly saw the patient with us at this time and recommended that an attempt should be made to remove the tumour.

Second operation.—May 20, 1929. Ether anæsthesia. The swollen spinal cord was once more exposed through the old wound. A posterior vertical incision was made in it slightly to the left of the middle line, partly because the surface vessels were rather more numerous on the right side and partly with the object of avoiding as far as possible injury of the nerve supply of the right hand. At a depth of 0·2 cm. the surface of a soft, grey tumour was encountered.

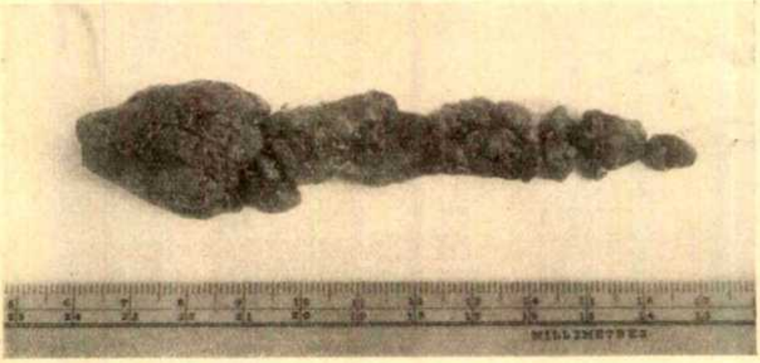

FIG. 3.—*Case* 1. Tumour after removal.

It was circumscribed and could be gently separated from the surrounding spinal cord by dissection with moist pledgets of cotton wool. This was rather tedious and the actual removal of the tumour took two hours. As shown in fig. 2, the tumour was first separated completely from the cord at its widest circumference, and was divided transversely. The upper portion was next removed, traction sutures being used to control its position during the dissection. The tumour narrowed at its upper end, where it was lying at a depth of 0·4 cm. from the posterior surface of the cord. When this part had been dislodged cerebrospinal fluid began to well up into the bed of the tumour. Removal of the lower portion was more difficult because here the tumour was narrower and softer. It was first of all necessary to extend the incision downwards. The spinous processes and laminæ of the second to fourth thoracic vertebræ were removed. The lower part of the tumour came away in fragments but the removal appeared to be complete (fig. 3).

After the tumour had been removed the part of the spinal cord which it had occupied appeared as a flat ribbon up to 2·5 cm. wide and covered by a thin film of blood-clot. The incision in the spinal cord was about 11 cm. long and was estimated to have extended from the fourth cervical to the third thoracic segment. It was impossible to close the dura, which was for the most part overlapped by the flattened spinal cord. The muscles and skin were closed with interrupted fine silk sutures. Apart from a slight fall of blood-pressure and rise of pulse-rate, there had been no appreciable change in the patient's condition throughout the course of the operation.

Pathological examination.—S.D. 1103, 1929. The tumour (fig. 4) after fixation measured 11 cm. long and up to 2·5 cm. in circumference, and weighed 14 grm. At the upper end was a conical depression 0·5 cm. deep (fig. 4*a*). The lower end was tapered like a bullet. The outer surface of the tumour was smooth. Its cut surface consisted of faintly lobulated soft tissue which was in places pink in colour and in others hæmorrhagic. Transverse sections of the tumour in its widest part showed a cleft 0·7 cm. by 0·15 cm. (fig. 4*b*) which extended into the upper portion of the tumour, where it divided into two smaller clefts. No cleft could be found in the lower, narrower part of the tumour. Histological examination showed an ependymal glioma (Plate III, fig. 5). The central cavity was lined by ependymal epithelium. Further remarks on the pathology of the tumour are given in the body of the paper.

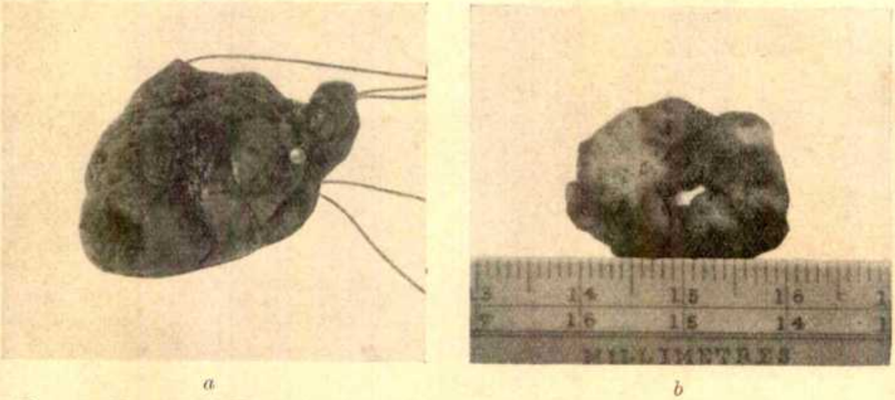

FIG. 4.—*Case* 1. (*a*) Upper portion of tumour to show conical depression in the extreme upper end. (*b*) Transverse section of tumour, showing central cavity.

Post-operative course.—The disturbance of spinal function after removal of the tumour was less than we had expected. There was no respiratory embarrassment. When the patient began to regain consciousness her pulse-rate rose rapidly from 120 to 170 and it remained at this level for four hours, falling gradually to normal during the next three days. The temperature did not rise higher than 99·6° F. For a few hours after operation the right thigh was warm, the left thigh cold. At this time also her left lower limb was completely paralysed and the movements of her left upper limb were very ataxic; the limbs on the right side were only slightly worse than before operation. Spontaneous lateral nystagmus was also observed during this period, and for the next five days both pupils were very small, the right being smaller than the left, and

PLATE III.

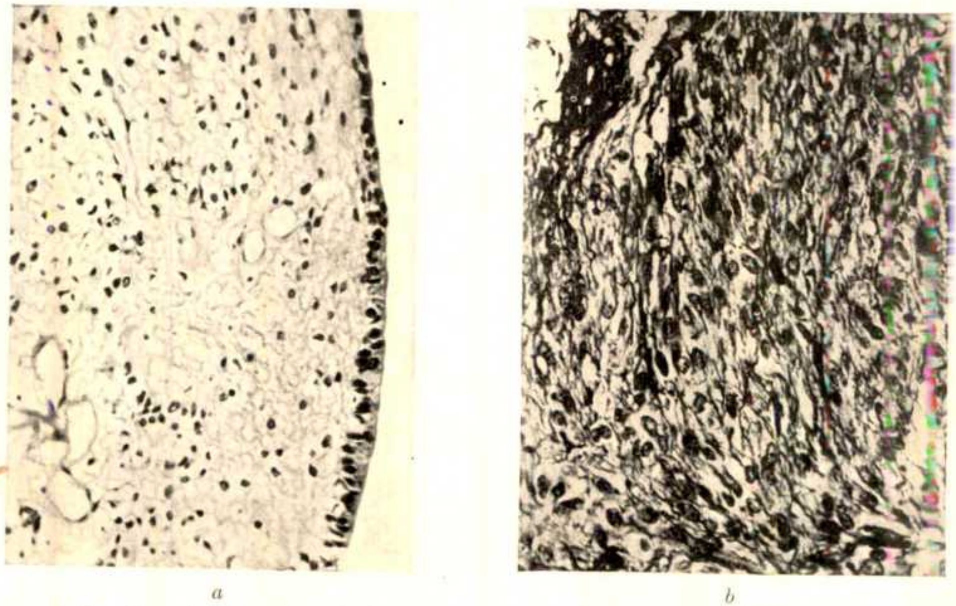

FIG. 5, *a*, *b*.—*Case* 1. Histological sections of tumour. (*a*) showing epithelium lining central cavity. Iron hæmatoxylin and van Gieson's mixture, × 175. (*b*) Showing ependymal spongioblasts. Heidenhain's iron hæmatoxylin, × 300.

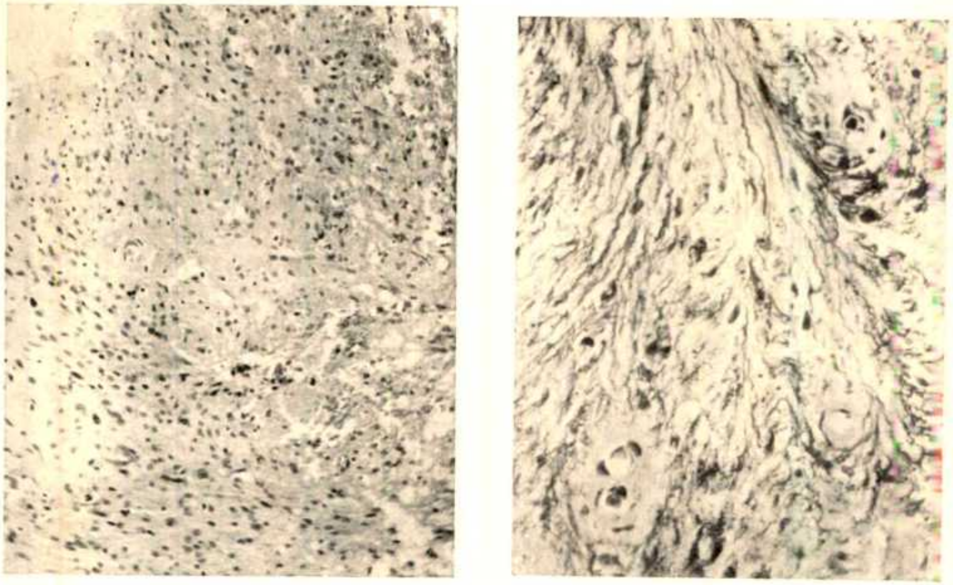

FIG. 10, *a*, *b*.—*Case* 2. Ependymal glioma. (*a*) Hæmatoxylin-eosin. (*b*) Phosphotungstic acid hæmatoxylin, × 450.

To illustrate paper by Hugh Cairns and George Riddoch.

there was considerable enophthalmos on both sides. For several days the knee-jerks were diminished, the ankle-jerks absent. The lower limbs were more flaccid than before operation. To our surprise the patient passed urine voluntarily and freely immediately after the operation; there was, however, increased frequency, and, as before operation, some urgency.

Convalescence was uneventful until the dressing was done on the tenth day when it was found that the centre of the wound was bulging. With the mistaken idea that there might be a hæmatoma a probe was inserted into this bulging area, and a leakage of cerebrospinal fluid was thus unfortunately established. Three weeks after operation the patient had what was evidently a slight attack of meningitis and also developed retention of urine and cystitis.[1] The leak continued intermittently for two weeks, but was then controlled by aspiration of the bulging area and by lumbar puncture, which incidentally showed that there was now a perfectly free flow of cerebrospinal fluid in the spinal subarachnoid space, and that therefore there was little likelihood of a second tumour in the lower part of the spinal cord. Eventually, on July 13, 1929, a further operation was done to repair the weakness of the scar, which was undoubtedly due to reliance on fine silk sutures for approximation of the muscles.

Recovery of voluntary power.—As noted above, the left lower limb was completely paralysed for a few hours after removal of the tumour, but thereafter voluntary power began to return. Movements of the right lower limb were but little affected. By the sixth day the patient could flex and extend her left lower limb at the hip and knee, but movements at the left ankle-joint were still very weak; her right lower limb was by this time quite as strong as it had been before operation. Recovery was evidently delayed by the attack of meningitis, for during the fourth and fifth weeks of convalescence no improvement occurred in the movements of her lower limbs. The patient walked for the first time ten weeks after removal of the tumour. She was discharged from the nursing home one week later. Walking was at first very imperfect owing to ataxia from loss of postural sensibility, weakness of her left lower limb and severe pain in her right knee. There was hyperextension of the knees on standing and occasional inversion of the ankles on walking. These disabilities gradually disappeared without the use of orthopædic appliances. By April, 1930, eleven months after removal of the tumour, she was able to walk a mile or more without any assistance, and soon was able to stand alone for long periods and to drive a motor car. When examined in July, 1930, her gait was still slightly ataxic and she was a little unsteady in performing Romberg's test, but these disabilities had entirely disappeared when she was last seen in March, 1931, twenty-two months after operation, and her walking was not restricted in any way. Movements of extension recovered before those of flexion, and her right lower limb recovered before the left, though when the patient was last seen voluntary power was equal in the lower limbs.

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[1] Cerebrospinal fluid, withdrawn by lumbar puncture on June 20, 1929, contained 130 white cells per c.mm.; finely granular oxyphils, 2 per cent.; lymphocytes, 90 per cent.; coarsely granular oxyphils, 8 per cent. Protein, ·055 per cent. Cultures were sterile.

Voluntary power of her upper limbs improved very quickly after removal of the tumour, recovery of the left side, the side that had been stronger before operation, lagging behind that of the right, doubtless because the incision in the spinal cord had been made to the left of the middle line. Within two weeks she was conscious of improvement in the strength of her hands, and six weeks after operation her handwriting became as good as it had been before the onset of her illness and she was able once more to do fine needlework. When she was seen twenty-two months after operation she said she could use her upper limbs freely and normally, but there was still some weakness and wasting of the small muscles of the hands and of the extensor carpi ulnaris on each side. Recovery of trunk movements followed the same sequence as that of the limbs. Five weeks after operation chest expansion was much better on the right side than on the left, and the right rectus abdominis contracted much more strongly than the left. Fourteen months after operation movements of the trunk were almost normal and equally strong on both sides.

Recovery of reflex function.—Immediately after operation the ankle-jerks were absent and the left knee-jerk was diminished. The right ankle-jerk was first elicited on the sixth day after operation and the left ankle-jerk returned one week later. Eventually the tendon-jerks of the lower limbs became slightly brisker than normal. In the upper limbs the tendon-jerks were all present after operation, but for some months they were diminished on the right side, and then became equal on both sides. The abdominal reflexes were first observed, on the right side only, six months after operation. At the last examination, twenty-two months after operation, the left lower abdominal reflex was diminished, but the others were brisk. At this time the left plantar reflex was still extensor, but only a flexor response could be obtained on the right side. Flexor spasms of the legs ceased after removal of the tumour, though for the first few days the patient had the sensation of slight spasms at the left knee.

Micturition was not affected by removal of the tumour, but when meningitis occurred the patient had increase in frequency, and then retention of urine, which persisted for eleven days. For a few weeks afterwards control of micturition was imperfect, and for some time there was urgency of micturition on excitement. The patient was averse to taking much fluid by mouth and her urine remained scanty (10 oz. per day), offensive, and contained pus and albumen, in spite of the fact that there was no residual urine. This trouble cleared up after the administration of large quantities of fluid by rectum. Nocturnal frequency persisted for some months, but eventually micturition became quite normal, apart from occasional attacks of urgency. The bowels had been constipated before operation and they remained so afterwards, though rather less aperient was necessary than before.

Recovery of sensation.—No accurate tests were made for some days after removal of the tumour, but there was evidently increased loss of postural sensibility of the left side, as indicated by the extremely ataxic movements of her left upper limb for some hours after operation. Numbness and tingling persisted in her right hand for twenty-four hours, but thereafter her hands felt normal, and her lower limbs also began to feel less heavy and stiff. There was for some months numbness of her legs on waking in the mornings.

Six days after operation, pin-pricks were appreciated in patchy fashion on her lower limbs up to the level of the first lumbar segmental area, and cutaneous analgesia on the arms began to diminish so that its upper level was difficult to define. The charts (fig. 1 *b, c.*) show the main features of sensory recovery. On the sixteenth day after operation complete anæsthesia to cotton wool was found in two distinct areas, an upper area from Th. 2 to Th. 9 and a lower area which extended from Th. 11 to the lower lumbar segments. This lower area was found to have disappeared completely when the patient was next examined on the forty-sixth day. Subsequently the area of anæsthesia to cotton wool was smaller than the area of analgesia to pin-prick.

The charts show that during the process of recovery there was considerable dissociation of sensibility to cotton wool and pin-prick and the recognition of written numbers, and they indicate that the return of sensibility to light touch and to pin-prick was fairly rapid and complete, except at and immediately below the segmental level corresponding to the lower portion of the tumour; whereas Zahlenschreiben and other forms of sensation conveyed by the posterior columns recovered very late. It is not surprising that the posterior columns were the last to recover, in view of their thinness as seen at operation and the manipulation that was necessary for removal of the tumour. For a long time, indeed, we were in doubt as to whether any appreciable recovery of postural sensibility would occur. Slight return of the appreciation of passive movement, but not of its direction, was evident at the right ankle six days after operation, and on the sixteenth day there was evidence of further improvement on the right side, but still complete absence of postural sensibility in the left lower limb. Six weeks after operation, however, it was found that there was no longer any appreciation of posture in the lower limbs. This retrogression was probably due to the attack of meningitis and cystitis which had set in in the fourth week after operation. It has been shown [14] that toxæmia from cystitis will depress the reflex functions of the spinal cord, and it is possible that conduction of the long tracts is also depressed at the same time. When the patient first began to walk she was very ataxic. No marked return of postural sensibility was observed until six months after the operation, when the patient began to appreciate the direction of movements at her knee- and ankle-joints, rather better on the right side than on the left. When examined, fourteen months after operation, she had accurate appreciation of passive movements and of their direction at the right ankle, and to a less degree at the left ankle, and postural sensibility was beginning to return in the toes. Twenty-two months after operation passive movements and their direction were appreciated normally at the right big toe and almost normally at the left big toe. For fourteen months after operation she had been quite unable to recognize numbers written on the skin anywhere below the third thoracic segmental level, but she then began to name correctly some numbers written on her right lower limbs. Twenty-two months after operation written numbers were recognized on the right side of the trunk down to the sixth thoracic segmental level, and were at times appreciated in both lower limbs (fig. 1 *c*). Vibration, however, was still not appreciated below the second thoracic segmental level. From the time of the first post-operative tests, postural sensibility, tactile localization, vibration and the recognition of numbers were perfect in the upper limbs.

The recovery of function of the spino-thalamic tracts was characterized by a dissociation in which the loss to cold was more extensive than to heat, and the loss to heat more extensive than that to pin-prick. The differences in extent of these areas of sensory loss were for the most part slight.

Sensations of tightness and prickliness occurred once in her lower limbs, about a year after operation, after the patient had walked a long distance, but they did not retnrn.

After operation the patient no longer suffered from cold feet as she had done before. Her toe-nails became much softer, but did not grow any faster. The right pupil remained slightly smaller than the left and its reactions to light and shade were rather sluggish.

Comment.—The result in this case may be considered satisfactory, though doubtless it would have been more rapidly attained, and without any infection of the bladder, but for the occurrence of slight meningitis during convalescence. The amount of recovery of spinal function, as the result of enucleation of the tumour, has been very considerable. The most surprising restoration has been in postural sensibility, in view of the unusual extent and severity of the loss in the lower limbs before operation, the extreme thinness of the posterior columns as observed at operation, and the interference with them that was necessary for removal of the tumour.

The encouraging result in this case prompted us to deal radically with yet another case that appeared a year later. As will be seen from the record that follows, the diagnostic problems were more difficult than in Case 1, and our inability to recognize that the tumour was intramedullary and not extramedullary before and during the early stages of the operation undoubtedly made the result less successful than it would otherwise have been.

Case 2. *Intramedullary ependymal glioma of thoracic spinal cord* (Th. 3—Th. 5). Initial symptom of severe "intercostal neuralgia." Complete removal of tumour at one-stage operation. Improvement.

History.—Mrs. C., aged 32, was referred by Dr. Warren Crowe on March 11, 1930, complaining of pain in the right side of the thorax and increasing weakness of her lower limbs. She had had no serious illnesses until February, 1929, when, after an attack of "influenza," she began to suffer from pain in the lower part of the right scapular region. The pain was at first dull in character and occurred in attacks lasting about one day and followed by two days of complete freedom. It was brought on or aggravated by bending, coughing and sneezing. As time went on the intervals between the attacks shortened. In June, 1929, it became much sharper and spread "straight through" the right side of the chest to the front at the same level. The pain was almost continuous, but violent attacks would come on suddenly and would last for five minutes at a time, during which she would stand quite still and hold her breast, and send her maid for aspirin. This pain was at times worse than labour pain. It was brought on or so aggravated by sitting that for six weeks she preferred to take her meals standing at the mantelpiece. Any attempt to stoop down made the pain worse, she was afraid to blow her nose, and she "lived in terror" lest she should get a cold. At nights she lay with a pillow under each scapula to relieve the soreness of her back. In August, 1929, six months after its onset, the pain became less severe, and she was able once more to sit down for meals. It now spread around the right side of the chest wall as a band about four inches wide. As the pain decreased in intensity, the patient became conscious of a tingling, itching sensation in the same area. The pain passed off in September, 1929, leaving only slight soreness.

During the period of pain the patient had been treated for "neuritis" by drugs, vaccines, extraction of teeth, electrical treatment and massage. In August, 1929, as the pain was diminishing, she thought she was getting better, but already she was having some difficulty in walking up and downhill. From that time onwards her lower limbs gradually became weaker. On one occasion her right knee gave way and she fell. By December, 1929, she could not walk without support and had to give up all her usual domestic activities. Her knees crackled very much as she walked. At this time she began to have a constant sensation as of a band of iron encircling the trunk at the costal margin, at a slightly lower level than the original pain, and more noticeable during walking. She now became conscious also of impairment of the sensation in her lower limbs. The lower limbs became increasingly heavy and troublesome, and flexor spasms occurred in the mornings. At the time of her admission to the nursing home in March, 1930, she could not walk or stand, though she could still move her lower limbs.

For six months before admission she had suffered from slight difficulty and delay of micturition. For four months her bowels, hitherto regular, had been very constipated, and on one occasion, one month before admission, she was incontinent of fæces. She had been troubled also with flatulent dyspepsia. Throughout the illness she had been conscious of a constant uncomfortable sensation of bodily heat, and she had also felt a loss of initiative and diminished emotional response.

Until the birth of her first child nine years before she had been slim, but subsequently had increased in weight.

Examination.—The patient was very stout and weighed nearly 15 st. (210 lb.). She was slow mentally but on the whole was a good witness. Her speech and articulation, discs, pupils and cranial nerves were normal. Her upper limbs also were unaffected. There was, however, marked weakness of her abdominal muscles and spastic paresis of her lower limbs, right more than left. The only abdominal reflex obtained was the left epigastric. Her knee- and ankle-jerks were much increased and the plantar responses were extensor.

At the fifth thoracic segmental level on the right side there was a zone of cutaneous tenderness below which cutaneous sensibility was lost. Sensibility to light touch was abolished over the front of the abdomen, but not on the back (fig. 6 *a*). There was complete analgesia to pin-prick from the sixth to the tenth thoracic dermatomeres and below this relative analgesia, except in the sacral areas where sensibility was almost normal (fig. 6 *b*). Sensibility to heat and cold were slightly diminished below the sixth thoracic level. Postural sensibility was completely lost in the toes and in the right ankle. Vibration, and numbers on the skin (Zahlenschreiben) were not appreciated below the fifth thoracic segmental level. The sensory disturbance was greater on the front than on the back of the trunk. There were no sensory changes in the upper limbs, but after lumbar puncture a dragged pin felt distinctly sharper above the second thoracic level than below it.

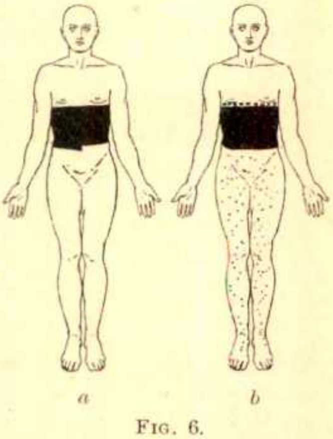


FIG. 6.

Palpation of the spinous processes of the second and third thoracic vertebræ produced deep-seated discomfort which persisted after pressure had ceased. The toe-nails were brittle and the patient stated that they had not grown at all for six months. Examination also showed a small post-anal dimple. X-ray examination of the spine was negative.

Lumbar puncture yielded a very slightly yellow fluid under a pressure of 195 mm. There was no rise of pressure on jugular compression, and after withdrawal of 6 c.c. of fluid the pressure dropped to 0. Protein, 0·075 per cent.; cells, less than 1 per c.mm. After the lumbar puncture there was recurrence of the sensation of soreness in the right scapular region that had been prominent some months before. No change occurred in the amount of paresis of the lower limbs.

Diagnosis—It was clear that there was spinal compression at the fifth thoracic level, but whether the tumour was within or without the cord was more difficult to decide. The presence of pain in the right side—at first posterior, then in addition anterior, and finally around the chest on that side over a fairly narrow zone associated with cutaneous tenderness—for six months before paraplegic symptoms began to appear weighed strongly in favour of an extramedullary localization. On the other hand, the fact that cutaneous sensory loss was greatest immediately below the situation of the pain and tenderness, and that it was bilateral and symmetrical, favoured a diagnosis of intramedullary tumour. We finally considered, and, as it proved wrongly, that the evidence indicated an intrathecal tumour outside the spinal cord at the level of the fifth thoracic posterior root on the right side.

Operation.—March 20, 1930. Ether anæsthesia. The first to sixth thoracic spinous processes were removed, but this large exposure subsequently proved to be unnecessary, for the lesion was fully displayed by removal of the third, fourth and fifth and the upper part of the sixth thoracic laminæ. When the dura was opened, the spinal cord presented as a fusiform enlargement about 5 cm. long. At the site of maximum swelling the cord was twice its normal size. It was pale and the vessels over its posterior surface were scanty, in contrast with the appearances above and below. Two delicate adhesions were found between the arachnoid membrane and the posterior surface of the cord. These were divided. The swelling was then aspirated by a fine needle, with negative results. The appearances suggested an intramedullary tumour, but the history, in our opinion, had so strongly favoured the diagnosis of an extramedullary tumour that it was considered unwise to incise the cord until its anterior aspect had been examined. Extramedullary tumours, as Elsberg [6] has pointed out, may sometimes become embedded in the anterior aspect of the cord so as to produce appearances simulating those of intramedullary tumour. The spinal cord was therefore thoroughly rotated to examine its right lateral and anterior aspects. There was no sign of tumour. Accordingly the right posterior column was incised, and at a depth of 0·15 cm. the surface of a cherry-red tumour was exposed (fig. 7). The tumour was circumscribed and, as it showed no signs of extruding itself, it was dissected out. By stroking its surface with pledgets of cotton-wool and with the points of fine dissecting forceps it was gradually freed, for it was but lightly adherent to the surrounding cord. As in Case 1, the upper end of the tumour presented a conical depression, and when this was tilted out a small amount of clear fluid came away from what was probably the dilated central canal of the spinal cord. The anterior surface of the tumour was rather more adherent than the rest, and at its centre was anchored to the spinal cord by a band of firm tissue, subsequently shown to contain numerous arterioles and veins. This was divided between silver clips (fig. 8). The tumour was then easily freed. In order to facilitate removal of its lower part, it was transsected below its centre and the upper part removed. The lower part was less adherent to the cord than any other part of the tumour.

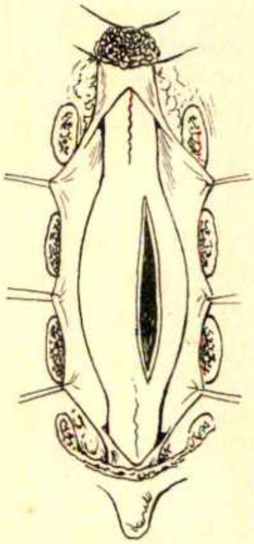


FIG. 7.—*Case* 2. Diagram of operation.

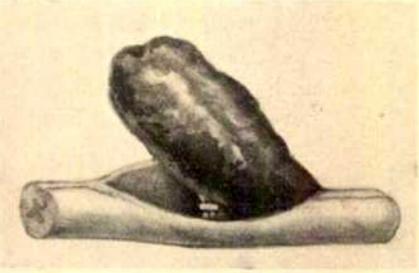
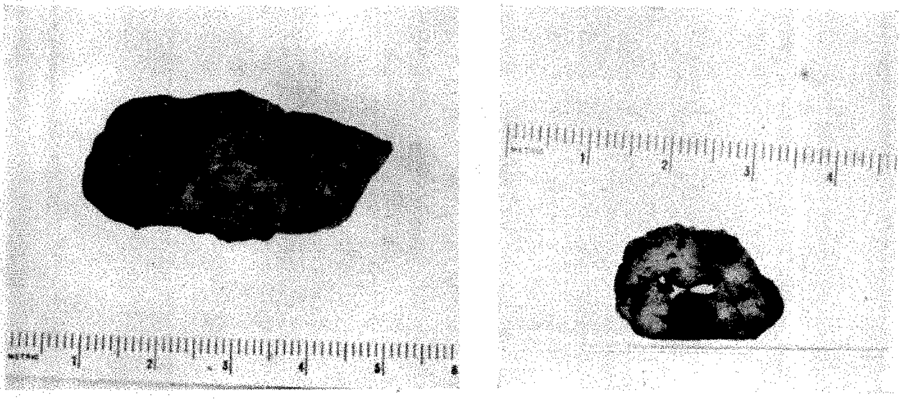


FIG. 8.—*Case* 2. Diagrammatic sketch of tumour being tilted out of the cord, showing vascular pedicle on anterior aspect of tumour. A silver clip has been placed on the pedicle.

The consistence of the tumour was firmer than in Case 1, and the position of the tumour during its removal could thus be controlled by dissecting forceps, without recourse to silk sutures. When the tumour had been removed, its bed appeared as a deep vertically directed cleft in the posterior aspect of the cord, covered by a film of blood-clot. Although the tumour measured over 2 cm. in its widest diameter, the groove was no more than 0·5 cm. wide, and it seemed remarkable that such a large tumour could have come out of this area.

The situation of the tumour, as shown by subsequent skiagrams of the silver clips which indicated the central point of the tumour, was in the third, fourth and fifth thoracic segments of the spinal cord. The tenderness that had been elicited by palpation of the spine before operation was immediately above the level of the tumour.

While the wound was being closed the pulse-rate rose above 170 and the blood-pressure could not be registered at the brachial artery. The patient became cyanosed and her extremities cold. A blood-transfusion was given, but there was no immediate improvement of her condition, and we formed the impression that the symptoms were not due to secondary anæmia but to manipulation of the spinal cord. The loss of blood during the operation had not been excessive.



a *b*

FIG. 9.—*Case* 2. (*a*) Tumour after removal. (*b*) Transverse section of tumour showing central cavity.

Pathological examination.—S. D. 678, 1930.—The tumour measured 4·5 cm. long and up to 2·2 cm. in transverse diameter (fig. 9). It weighed 5·6 grm. after twenty-four hours' fixation. Its upper end presented a conical depression, 0·4 cm. deep. The lower end narrowed rapidly to a sharp point. The surface of the tumour was smooth, but to it were adherent a few delicate strands of tissue. These, it was thought, might consist of nerve-fibres, but histological examination revealed no normal nervous tissue. On its anterior surface there was a smooth shallow slit-like depression, 1·1 cm. long. The tumour was composed of greyish-white glistening tissue in which were numerous areas of hæmorrhage. Sections showed a transversely placed cleft, 1·2 cm. wide and 0·2 cm. in an antero-posterior direction, which was continued upwards to open on the surface at the apex of the conical depression in the upper end of the tumour. There was a second and separate cleft, 0·5 cm. wide, in the lower part of the tumour. Histological examination showed an ependymal glioma (Plate III, fig. 10). No trace of ependymal epithelial lining could be found in the clefts. Their walls were formed by the tissue of the tumour.

Comment.—As will be seen from the notes that follow, the result in this case has not been so far as satisfactory as in Case 1. This may be due in part to the fact that the mid-thoracic cord, being smaller than the cervical cord, is more likely to be seriously injured by operative interference. We feel, however, that the main reason lies in the fact that during the operation the cord was freely rotated for examination of its right antero-lateral aspect. Though rotation of a normal cord can be accomplished without any subsequent disturbance of spinal function, the same procedure must surely be more dangerous when the fibres of the cord are already tightly stretched over an intramedullary tumour. In this case the great delay in recovery of the right lower limb was almost certainly due to damage of the right pyramidal tract during rotation of the cord.

The operation was done in one stage mainly because the patient was so very heavy and obese, not a suitable subject for multiple operations. Moreover, her condition throughout the removal of the tumour, as indicated by five-minute records of the blood-pressure, pulse and respiration rates, did not at any stage indicate that the operation should be abandoned.

Post-operative course.—The general condition of the patient rapidly improved and gave no anxiety. The temperature did not rise above 101° F. However, it was at once evident that there was serious disturbance of spinal function. There was complete paralysis and loss of sensibility in her lower limbs, loss of knee- and ankle-jerks, and retention of urine. She felt that her lower limbs were in a position of acute flexion. Flexor and extensor spasms of the lower limbs were more numerous than before operation.

Recovery of voluntary power.—On the third day after operation very feeble voluntary movements of the left hip and knee were first observed. For several days, however, these movements could only be performed at times and were immediately fatigued, and it was not until nearly three weeks after operation that the patient could voluntarily raise her left knee from the bed. One week later slight voluntary movements began to return in the right lower limb, consisting of adduction and extension at the right hip-joint. Voluntary flexion of the right knee was first observed eight weeks after operation; it was not until three weeks later that there was any voluntary movement of the toes of the right foot. She stood by herself and walked a few steps with assistance for the first time twelve weeks after operation. Movements of the left lower limb were by this time fairly good, but movements of the right lower limb were still feeble and inco-ordinate, and the limb was very spastic. In walking there was great inversion of the right ankle, and to prevent this a light walking iron was applied. The patient was discharged from the nursing home on June 29, 1930, fourteen weeks after operation. For some months she made very little progress with walking, but when last seen, nine months after operation, she was able to walk fairly well with sticks and was beginning to walk a little without them. She had resumed the management of the house and carried out all indoor activities unaided, but she still preferred to make her outdoor journeys in a wheel-chair. Doubtless her great weight, and also a want of effort, retarded her recovery. Examination at this time showed that voluntary power and tone of the left lower limb were normal, but there was still great weakness of flexion of the right lower limb which was very spastic. Her abdominal muscles recovered first on the left side, but subsequently the right side of the abdominal wall became just as strong.

Recovery of reflex function.—Immediately after operation all the reflexes below the level of the lesion were absent, but within twelve hours an extensor plantar response was obtained on each side, more active on the left than on the right side. These became more brisk in the next twelve hours and at the same time flexor and extensor spasms of the lower extremities began to occur. A feeble right knee-jerk could be obtained on the third day after operation, and the left knee-jerk was first elicited on the following day. These reflexes became quite brisk in the next four days. The right ankle-jerk was first observed three weeks and the left ankle-jerk five weeks after operation. Later the tendon-jerks of the lower limbs became exaggerated, especially on the right side, where there was also sustained ankle clonus. Five weeks after operation the spasms were mostly extensor in type and mainly limited to the right lower limb. These spasms subsequently increased, but were partially controlled by luminal. Fourteen weeks after operation they became less frequent and within two weeks had practically disappeared. The left upper abdominal reflex was first observed fourteen weeks after operation. When the patient was last seen nine months after operation the abdominal reflexes, with the exception of the right upper abdominal reflex, were all present. The plantar reflexes were extensor, and there was also a flexion reflex of the left lower limb which could be elicited by any nocuous stimulation on the left side below the tenth thoracic level. The right knee- and ankle-jerks were exaggerated and sustained clonus could be evoked at the right ankle. The tendon-jerks of the left lower limb were brisk.

After the operation there was complete retention of urine, for which a catheter was passed every six hours. On the seventh day the patient could feel the catheter and became conscious of the filling and emptying of her bladder. On the ninth day she had a violent pain and a sensation of fullness in the region of the bladder. Although the bladder had been supposedly emptied by catheter three hours before, 22 oz. were now drawn off and the urine was offensive and contained pus and bacteria. The discomfort lasted only a few hours, but the urine remained turbid for some days. The patient passed small amounts of urine naturally for the first time three weeks after operation. Voluntary micturition gradually improved so that two months after operation the amount passed naturally exceeded the amount obtained by catheter. Five months after operation the residual urine had diminished to 2 to 3 oz. Catheterization and bladder washes were stopped shortly afterwards. Nine months after operation the residual urine was less than 1 oz., the frequency was normal and there was no urgency or incontinence. The urine, however, still contained pus and bacteria.

During the first days of convalescence the bowels were moved daily by enema, given while the patient was on a bedpan, for she had no control of the rectal sphincters. She began to regain control of defæcation for the first time about four weeks after operation, and from then on she steadily improved in this respect and was soon better than she had been before operation. On discharge from the nursing home there was no incontinence or urgency of defæcation, and the constipation from which she had suffered before operation was no longer present. The indigestion also did not return.

Recovery of sensation.—Immediately after operation there was complete sensory loss in the lower limbs. Twelve hours later pin-prick could be appreciated on the legs as a touch, but then for a few hours anæsthesia became once more complete, possibly as a result of œdema of the spinal cord at the site of operation. On the third day after operation there was complete cutaneous anæsthesia of the trunk, and some cutaneous analgesia over both lower limbs, especially the left, where there was also gross loss of tactile localization,

Subjective sensory disturbances were prominent. In the first two days after operation the patient felt a warm, tingling sensation in both groins and in the right heel. On the fourth day she began to have fairly severe pain behind the right shoulder aud examination showed a zone of severe cutaneous tenderness in the second to fourth thoracic segmental areas on the right side and the second to fifth segmental areas on the left side. Both pain and cutaneous tenderness were more intense on the right side. The pain was aggravated by spasms of the lower limbs. It decreased considerably in severity after five days, but persisted in slight degree on the right side for some months, and then disappeared. The cutaneous tenderness disappeared ten days after operation.

The recovery of sensation was much slower than in Case 1, and it also differed in presenting some disparity between the two sides, which we attribute to injury of the right antero-lateral tract and posterior column at operation. The ability to appreciate and localize pin-prick, heat and cold returned first in the right lower limb, while recovery of postural sensibility and appreciation of light touch returned first on the left lower limb. Of all sensory qualities light touch was the first to recover. Recovery of painful and thermal sensibility occurred first in the sacral dermatomeres and advanced in a headward direction; and during recovery there was some dissociation at the lower limits of sensory loss where pin-prick was appreciated before heat, and heat before cold. On several occasions inversion of temperature sense was observed at both the upper and lower limits of sensory loss, cold being felt as hot over the fifth and sixth thoracic segments and the lower lumbar segments on the right side. There was no evidence of recovery from the upper limit of sensory loss in a caudal direction.

The first sign of return of postural sense in the lower extremities was observed five weeks after operation when the patient began to recognize the direction of passive movements of the left knee. In the next nine weeks there was no appreciable improvement of postural sense in the lower limbs, but when the patient was again examined six weeks later, that is five months after operation, a great improvement was observed. The direction of movements of the left knee and of most movements of the left ankle was now recognized. At this time there was no recognition of the direction of movements in the right lower limb.

When the patient was last examined nine months after operation there was anæsthesia to cotton wool from the sixth to eleventh thoracic segmental areas, complete analgesia to pin-prick from the fifth thoracic to first lumbar segmental areas and relative analgesia from the first to third lumbar segmental areas. Below this level pin-prick was still appreciated better on the right than on the left side. The loss to heat extended from the sixth thoracic to the fourth lumbar segmental area on the left side and to the fifth lumbar segmental area on the right side; loss to cold from the sixth thoracic to the first sacral segmental area on the left side and to the fifth lumbar segmental area on the right side. Passive movement and position were recognized at all joints of the left lower limb, but no improvement had occurred in the right lower limb. There was still complete inability to recognize written numbers below the fifth thoracic segmental level.

One week after operation a lumbar puncture had been performed as we felt that it was particularly desirable to know at that stage whether there was a likelihood of multiple tumours. The resting pressure was 210 mm. of cerebrospinal fluid. On jugular compression the pressure rose rapidly to 300 mm. and there was a similar abrupt fall to 200 mm. when pressure on the jugular veins was released. It was thus clear that there was little likelihood of a second tumour.

PATHOLOGY.

We do not propose to consider in detail the histology of ependymal gliomas. In our cases the tumours were composed of leashes of cells possessing tails that radiated towards connective tissue trabeculæ and vessels. The cells had no footplates, and specific stains showed that they contained blepharoplasten and fibrils. Both tumours were undoubtedly ependymal gliomas. They were quite circumscribed, but histological examination showed no capsule of connective tissue; instead, the tumours were bounded by a layer of compressed fibrillary neuroglia. Reticulum was limited to the blood-vessels, which were most numerous in the superficial parts of the tumours.

At operation that part of the spinal cord which contained the tumour presented a fusiform swelling, and in Case 1 there was slight bluish and yellow discoloration of the posterior columns at the site of maximum swelling. Each tumour was connected with the surrounding spinal cord by delicate strands of tissue which could be easily broken at operation by dissection with moist pledgets of cotton wool, or with the points of dissecting forceps. Presumably, these strands of tissue were neuroglia. In Case 2, inspection of the outer surface of the tumour after operation suggested that on it might be some fragments of nervous tissue; however, histological examination showed no nerve fibres but only neuroglia. Sections of necropsy material suggest that there is no serious risk of removing nerve fibres during careful surgical dissection of one of these tumours; around the tumour a zone of gliosis is commonly found and where such a zone is absent the adjacent white matter appears to have undergone degeneration.

Each of these tumours contained one or more cavities, but, whereas in Case 1 the large cavity was lined by ependymal epithelium, in Case 2 the cavity had no such lining, but only walls of tumour tissue. A vascular pedicle was found on the anterior aspect of the tumour in Case 2, and this appears to have provided the main blood supply of the tumour, also the only point of firm attachment. No vascular pedicle was found in Case 1.

Our observations at operation suggest that the tumour extends mainly in a downward rather than in an upward direction, for we found in both cases that the tumour was narrowest, softest and least adherent at its lower end. In each case the upper pole of the tumour presented a depression resembling the uterine cervix in miniature and this portion of the tumour was quite free from attachment to the adjacent spinal cord; and when, during the process of dissection, it was tilted out of its bed, a small amount of clear fluid escaped from the interior of the spinal cord above it. There was no justification for investigating further at operation the reasons for this depression at the apex of the tumour, but the most reasonable inference is that it was produced by fluid under pressure in the dilated central canal of the spinal cord. It is probable that an intramedullary glioma of this type may obstruct the downward flow of cerebrospinal fluid in the central canal of the spinal cord and so produce a slight degree of hydromyelia in those spinal segments that lie immediately above the tumour (fig. 11). Post-mortem investigations of spinal cords containing ependymal gliomas would help to settle this point. In this connection it is interesting to note that Kronthal [12] found dilatation of the central canal in dogs after gradual compression of the spinal cord.

It is important to recognize that ependymal gliomas of the spinal cord may be multiple or may be associated with syringomyelia in other parts of the spinal cord [11]. When multiple there may also be tumours of the nerve roots of the spinal cord. There are several examples of these combinations in the records of the Pathological Institute of the London Hospital and these are being made the subject of further study.

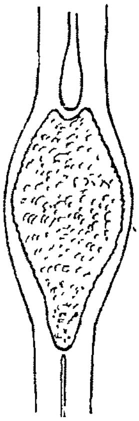


FIG. 11.—Diagram of intramedullary ependymal glioma to show the depression found in the upper pole of the tumour, and the slight hydromyelia which appeared to have been present above the lesion.

SYMPTOMATOLOGY.

There is no need to stress the desirability of accurate diagnosis before operation in cases of this type. Failure to make this in Case 2 limited considerably the success of the post-operative result, though probably with greater experience of the appearances of spinal tumours at operation the second mistake, of not at once recognizing from the appearances presented that the tumour undoubtedly lay within the cord, may in future be avoided. These cases presented certain similarities of symptomatology, of which girdle sensations below the level of the lesion and numbness of the perineum may be worthy of note. It is in their contrast, however, that their main interest lies. In Case 1, pain was a relatively insignificant symptom and was referred to the back of the neck at the level of the tumour; in Case 2, on the other hand, pain of great severity confined to the right fifth thoracic segmental area was the only symptom complained of by the patient for the first six months of her illness. Pain is a fairly common symptom of intramedullary tumours, but the occurrence of such a severe radicular type of pain is not a well-known phenomenon. Foerster [8] has observed it in several cases and Schultze [15] has also reported a case in which it dominated the clinical picture. It appears from the literature that it is most likely to appear with intramedullary tumours in the thoracic portion of the cord. Similar pain has been frequently observed by Wilfred Harris [10] in the initial stages of intramedullary gliosis "before any muscular wasting or even before analgesia or 'thermanæsthesia can be detected," and Foerster [8] has described a remarkable case in which, through a period of years, gliosis gradually spread through one side of the lower cervical cord, segment by segment, producing successively in the corresponding segmental area first hyperalgesia and spontaneous pains, and then analgesia with relief from pain. There is little doubt but that irritation of the region of the posterior horn can produce a pain that in every way resembles "root" pain, and in this connection it will be recalled that Dusser de Barenne [4] has shown that the application of strychnine to the posterior horns in an animal causes very definite paræsthesia in the skin corresponding to the segment of spinal cord that is excited, even after degeneration of the corresponding posterior root. This, however, may not be the invariable explanation of pain like that noted in Case 2. Foerster [8] considers that in some of his cases of intramedullary tumour the "radicular" pain was due to associated adhesions of the arachnoid ("arachnitis"). In our Case 2, two adhesions were found at operation between the posterior surface of the cord and the overlying arachnoid, but these were so delicate, and were moreover so nearly situated in the mid-line, that it is unlikely that they were responsible for the right-sided neuralgia. A thorough examination of the right lateral aspect of the cord was made and no other adhesions were found. We believe, therefore, that the pain in Case 2 was not due to arachnoideal adhesions, but was of intramedullary origin.

The physical signs of intramedullary tumours are probably of more value in diagnosis than the symptoms, though none of them when taken singly may be considered pathognomonic. Attention should be directed rather towards the *combinations* of physical signs that are suggestive of an intramedullary tumour. Signs of a lesion of considerable longitudinal extent in combination with dissociated sensory loss in the areas supplied by the affected segments are suggestive of an intramedullary tumour. This combination occurred in Case 1, where the lesion evidently extended from the fourth cervical segment (the upper limit of sensory loss) to the first thoracic segment (the lowest limit of observed atrophic palsies). In the parts supplied by these segments there was loss of sensibility to pain, heat and cold with preservation of sensibility to light touch and passive movement; below these segments there was complete sensory loss except in the sacral areas.

In the presence of incomplete sensory loss in the lower limbs, an area of anæsthesia, or of severest sensory loss, on the trunk, which extends up to the region of pain and cutaneous tenderness, suggests an intramedullary lesion. This combination of signs occurred in Case 2.

Severe tonic spasms of the lower limbs at a time when the disturbance of the pyramidal tracts is incomplete is regarded by Foerster [9] as a fairly common sign of intramedullary tumour. This combination of signs was present in each of our cases.

Lumbar puncture yielded yellow cerebrospinal fluid in both our cases and Queckenstedt's test demonstrated a blockage of the subarachnoid space. In Case 1 there was severe aggravation of the symptoms after lumbar puncture, but in Case 2 only slight change followed lumbar puncture. In each case complete relief of blockage of the subarachnoid space was effected by removal of the tumour, as was shown by lumbar puncture after operation.

THE EFFECTS PRODUCED BY REMOVAL OF INTRAMEDULLARY TUMOURS.

In both our cases removal of the tumour was followed by tachycardia, but in Case 1, at least, it was no more than the usual reaction that follows cervical laminectomy, for an exactly similar tachycardia had been observed after the first operation when, except for attempted aspiration with a fine needle, the cord itself was not interfered with. Tachycardia after laminectomy is a reaction that needs closer study. From our experience we believe that it is not due to hæmorrhage and this is borne out by Case 2, in which blood transfusion had not the slightest effect of slowing the pulse-rate or in other ways improving the patient's condition. In Case 1 on both occasions the reaction, an abrupt rise of pulse-rate from 120 to 170, occurred *after* the conclusion of the operation and coincided with the recovery from ether anæsthesia.

Records of the blood-pressure were made at intervals of five minutes during the operations, and they did not show any sudden fall of pressure such as de Martel [13] has observed during manipulation of the cord. In neither case was there any severe rise of temperature after removal of the tumour. In Case 1 the rectal temperature rose to 99·4° F., in Case 2 to 101° F.

It is interesting to observe that in Case 1 the removal of tumour tissue as high as the fourth cervical segment was not attended by any serious respiratory disturbance, for it has been stated [6] that there is danger of sudden death from paralysis of the phrenic nerves during intramedullary operations at this level. In our case the upper pole of the tumour was very loosely connected with the spinal cord and, apart from the incision in the left posterior column, only the gentlest dissection was necessary to enable this part of the tumour to be tilted out. During this stage of the operation the respiration rate rose from 25 to 30, but subsequently fell again.

Interference with the cervical cord in Case 1 produced temporary increase of the ptosis, enophthalmos, and miosis observed before operation, and thus evidently gave rise to increased disturbance of the central connections of the cervical sympathetic. No disturbance of sweating was observed. In a case of angioma within the first thoracic segment operated on by Garrè, Schultze [15] reports that there was profuse sweating of the whole of the patient's face, with the exception of the chin, during the operation.

The only other effect observed from incision of the cervical and upper thoracic cord in Case 1 was severe ataxia of the left upper limb. The incision, it will be recalled, was made through the left posterior column. This ataxia cleared up within a few hours and thereafter no abnormality of the function of the posterior columns could be detected in the upper limbs. It is to be noted also that in this case there was no disturbance of micturition from incision of the cord.

Foerster [8] has observed hyperalgesia, pains and paræsthesias after incision of the posterior columns. Thus, in a case of intramedullary cyst of the cervical cord an incision was made in the right column of Goll of the third and fourth cervical segments, and afterwards hyperalgesia was found in the right lower limb and right half of the abdomen up to the level of the xiphisternum, and the patient complained at times of severe paræsthesias and pains in the hyperalgesic area. No such striking symptoms occurred in our cases. In Case 1, in which the left posterior column was incised from the fourth cervical to the third thoracic segment, there was complete freedom from unpleasant sensory phenomena of this type after operation. In Case 2, in which the right posterior column was incised from the third to fifth thoracic segment the patient complained twenty-four hours after operation of a warm tingling feeling in both groins, and a sensation in the right heel which she described as "a mixture of pain and normal sensation." These disappeared in a few days. On the fourth day after operation she complained of pain in the right shoulder and was found to have a zone of cutaneous tenderness which extended on the right side, where it was extreme, from the second to fourth thoracic, and on the left side from the second to fifth thoracic segments. This cutaneous tenderness disappeared after a few days leaving very slight relative analgesia. The pain also became much less, but still recurred on occasions for several months.

This zone of cutaneous tenderness corresponded almost exactly with the level and extent of the incision in the cord, but cannot be ascribed to incision of the right posterior column about 1 mm. from the middle-line. It is much more likely to have been due to irritation of the posterior horns themselves and to have been of the same order as the neuralgic pain in the right fifth thoracic segmental area that was such a prominent feature of the early stages of the illness. It is curious, however, that this zone should have occurred at a higher level than the original neuralgic pain. It appears from the history and from the physical signs when the patient first came under our notice that before operation spontaneous pain was severe and cutaneous tenderness slight, whereas after operation pain was not severe but cutaneous tenderness was very acute.

RECOVERY AFTER THE REMOVAL OF INTRAMEDULLARY TUMOURS.

These cases show that a considerable degree of recovery of spinal function may be expected after the removal of circumscribed intramedullary tumours. As the case reports show the recovery is essentially gradual: it was still progressing in Case 1, when the patient was last examined twenty-two months after operation. The function of the posterior columns below the second thoracic level, which had been completely lost before operation, did not show any sign of recovery until six months after operation, and it was still improving when the patient was last examined.

All forms of sensation recovered in an upward direction, though in Case 1 there was also slight recovery at the upper limit of sensory loss in a caudal direction. Case 2 is of little value in analysing the recovery of sensory function, for this is not as yet sufficiently advanced and the observation is marred in this, as in other respects, by injury of the right side of the cord during the operation. Case 1, however, shows several points of interest. In this case the recovery of sensibility to cotton wool, pin-prick, heat and cold was rapid in the lower limbs and lower part of the trunk, and much slower and incomplete in the upper part of the trunk. On one occasion the area of anæsthesia to light touch, which before operation had extended up to the second thoracic level, was found to have resolved into two separate areas, an upper area from the second to ninth thoracic segmental areas, and a lower area which extended from the eleventh thoracic to the lower lumbar areas. Subsequently the lower area disappeared completely and rapidly, while the upper disappeared much more slowly. The anæsthesia in distal parts was clearly due to pressure on the long afferent tracts. Observations before operation, though incomplete, suggest that it appeared at a relatively late stage of development of the tumour. During recovery painful stimuli were appreciated before heat, and heat before cold.

Recovery of voluntary power after removal of the tumours occurred in the extensor muscles before the flexors. Reflex function distal to the lesion was temporarily depressed in Case 1, and temporarily abolished in Case 2, after removal of the tumour. Trophic changes in the paralysed parts were very slight before operation, but in both cases after removal of the tumour there was distinct evidence of improvement, as judged by the condition of the toe-nails, which became less brittle and grew more freely.

TREATMENT.

Successful results from the removal of intramedullary tumours at operation have been reported by Eiselsberg and Ranzi [5], Elsberg [6], Foerster [8, 9], and others, but the modern tendency appears to be towards more conservative measures, either operation by the method of extrusion, or X-ray treatment. From experience with these two cases we wish to urge that operative enucleation of the tumour has its place in the treatment of at least some cases of intramedullary tumour. In our opinion the method advocated by Elsberg and Beer [7] and known as the method of extrusion is not suitable for cases of the type we have described, for from observations at operation it was clear that these tumours would not have extruded themselves appreciably, as they were connected to the surrounding cord by numerous glial adhesions. Some intramedullary ependymal gliomas may be so soft that they can be removed by suction without any damage to the cord, as in a case reported by Cushing [2], but in our cases suction was found to be ineffective and we feel that the subsequent course of both patients has demonstrated that removal of the tumour by gentle dissection was the most suitable method of attack. Furthermore, perusal of Elsberg's own cases [6] shows that his most successful result, in a tumour closely resembling that of Case 1, was obtained by almost the same methods that we have followed. We feel that there have perhaps grown up around this "method of extrusion" misconceptions that were not originally intended by Elsberg himself. The method doubtless has its uses, but not for all cases of intramedullary tumour.

In a recent monograph Jonesco-Sisesti [11] recommends that treatment should be by means of X-rays, with or without a preliminary decompressive laminectomy. This author has collected nineteen cases of intramedullary tumour associated with syringomyelia and he affirms that surgical removal of the tumours is not practicable, but that X-ray treatment is followed by remarkable success. Bailey and Bucy [1] have also reported considerable improvement in a case resembling our Case 1 after decompressive laminectomy and X-ray treatment. It is difficult for us to compare our cases, in which, of necessity, only a limited examination of the cord was made, with those of Jonesco-Sisesti. He implies that all intramedullary tumours are associated with syringomyelia. It seems fairly well established that syringomyelia may be present above an intramedullary tumour without giving rise to any symptoms, and, though in our cases the clinical course of the disease was rather more rapidly and steadily progressive than in most of the cases described by Jonesco-Sisesti, it is not possible for us to be certain that they do not belong to the group he describes. In any event we feel that the claims he has made for X-ray treatment as opposed to surgical removal of the tumour are by no means fully established, especially in the light of the case of Dowman and Smith [3], in which at successive operations a syringomyelic cavity was evacuated and an intramedullary ependymal glioma was removed, with complete success. The best method of treatment of the various types of intramedullary tumour must for the present remain an open question.

SUMMARY.

Two cases of intramedullary ependymal glioma of the spinal cord are described. In one the tumour extended from the fourth cervical to third thoracic segments; in the other from the third to fifth thoracic segments. Both tumours were completely removed at operation with good result. The clinical features of the cases, which differed greatly in symptomatology, are discussed and the immediate effects of operation and results of treatment are reported in detail.

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A CONTRIBUTION TO THE NEUROPHYSIOLOGY OF THE URINARY BLADDER IN MAN.

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INTRODUCTION.

THROUGHOUT this paper the term "sympathetic" will be used to denote that part of the autonomic system which leaves the spinal cord in the thoracicolumbar region, whereas the term "parasympathetic" will be used for the part of the autonomic system leaving the sacral region of the cord.

In the course of surgical operations for the relief of certain vesical conditions, I have had a unique opportunity for making direct observations on the sympathetic control of the urinary bladder. These observations, together with a study of the physiology of the bladder after sympathetic neurectomy, form the basis of this report. By analysing my data, I have been able to clarify certain neurophysiological aspects of vesical function. The paper is strictly confined to the physiology of the human being; it follows that there has been little opportunity for multiplying observations. It is true that in recording the results of observations upon human beings a worker has the great advantage of being able to converse with his subject, so that much may be made of any one opportunity. On the other hand, he cannot make full use of the many instruments of precision available for recording physiological changes during experiments upon animals; nor can he consistently use the fruitful method of degenerative nerve section.

It is a pleasure to record my thanks for the helpful co-operation of my colleagues of the Section on Urology of The Mayo Clinic. On many occasions they have, at my request, consented to subordinate their own interest in the subject by making observations in ignorance of what was being done, or had been done, to the various vesical nerves.

PART I.—THE PHYSIOLOGICAL ANATOMY OF THE NERVES OF THE BLADDER.

It is essential to introduce this section because of inaccuracies in the description usually given in current textbooks of physiology. The majority of the sympathetic nerves for the pelvic viscera, including those for the urinary bladder, pass through a "bottle neck" in front of the sacrum, where they are collected together as the presacral nerve [10] or superior hypogastric plexus [9]; this forms a convenient point of departure. The presacral nerve has three roots: a right and left lateral, and a middle (fig. 1). On the right side the lateral root begins about 1·5 cm. below the right renal artery, by the union of three or four nerve bundles of constant origin [11]. The most internal arises from a nervous loop which crosses the aorta below the origin of the superior mesenteric artery; the middle springs from the semilunar ganglion or cœliac plexus, the external from the right periarterial renal plexus; these twigs unite to form a single small filament. As this passes downward it is joined on its outer side by two branches arising from the first and second lumbar ganglia respectively. Most of the fibres of the original root pass to the intermesenteric and inferior mesenteric plexuses; the remainder, with the branches from the lumbar ganglia, continue their downward course and reach the interval between the common iliac arteries as the right lateral root of the presacral nerve.

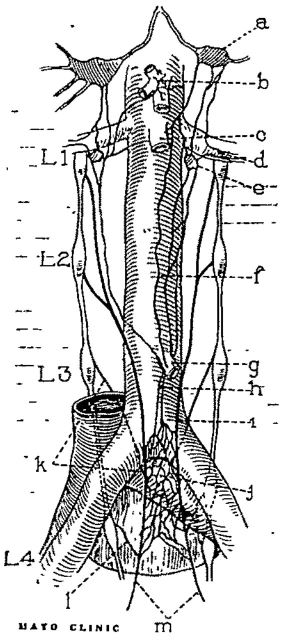
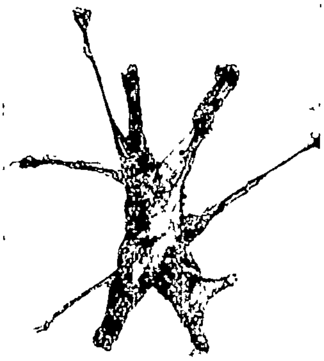


FIG. 1.—Connections of the presacral nerve: (*a*) semilunar ganglion; (*b*) cœliac plexus; (*c*) superior mesenteric artery; (*d*) renal plexus; (*e*) renal ganglion; (*f*) intermesenteric plexus; (*g*) inferior mesenteric artery; (*h*) middle root of presacral nerve; (*i*) left lateral root of presacral nerve; (*j*) presacral nerve; (*k*) branch from third lumbar ganglion: (*l*) branch from fourth lumbar ganglion; and (*m*) hypogastric nerves. (After Laux.)



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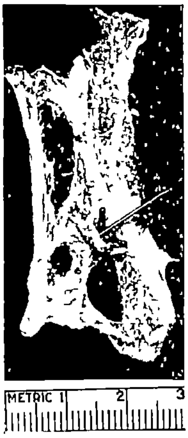
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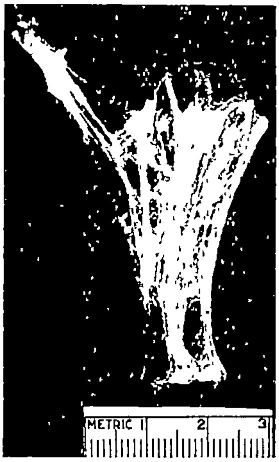
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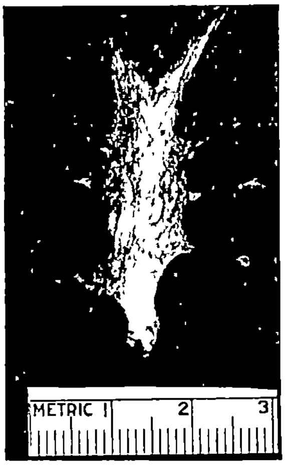
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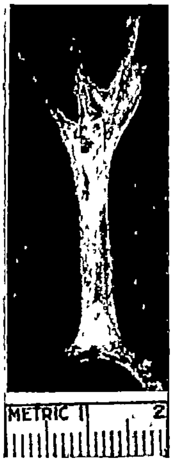
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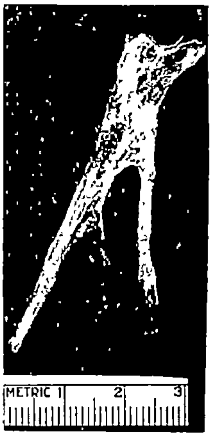
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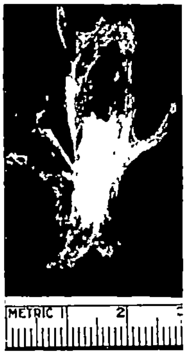
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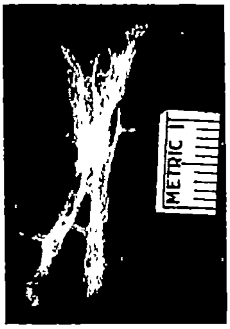
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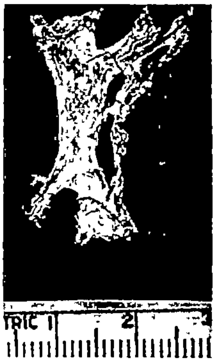
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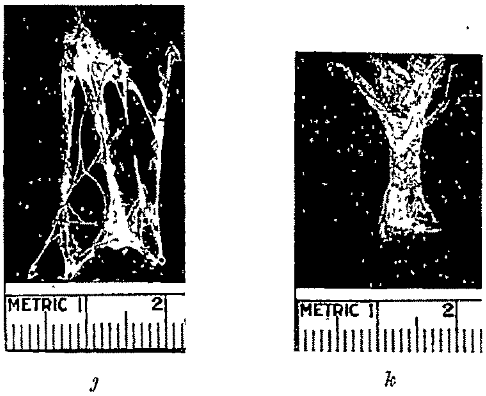

FIG. 2.—Types of presacral nerve: (a) above on the right, branches from first and second lumbar ganglia; on the left, these branches are united to form one trunk. On each side are the branches from the third and fourth lumbar ganglia. Below are the two hypogastric nerves; (b) the tip of the arrow lies under the union of the branches from the third lumbar ganglia, which enters the nerve posteriorly; (d) solid type; (j) plexiform type. Central end of nerve at top

The left lateral root of the nerve has a similar origin. The middle root is the prolongation downward of the intermesenteric plexuses, after they have supplied the roots of origin of the inferior mesenteric nerves; these intermesenteric plexuses establish wide connections with the cœliac, semilunar and aortico-renal ganglia. The middle root of the presacral nerve is received into the angle of convergence of the lateral roots. The presacral nerve itself is subject to wide variations in form (fig. 2); usually it is stated to be more or less solid in 20 per cent. of cases, and plexiform in the remaining 80 per cent.; however, according to my own experience, these figures should be interchanged. The nerve receives additional communications on each side, from the third and fourth lumbar ganglia; in the specimens which I have examined the branches from the third lumbar ganglia usually united to form a single filament which entered the posterior aspect of the nerve (fig. 2 (*b*)). From a histological standpoint (fig. 3) the majority of the fibres springing from the lumbar ganglia are medullated, whereas the fibres of the middle root are non-medullated; the former make up about 60 per cent. of the total fibres of the presacral nerve, the latter about 40 per cent. A few ganglion cells are to be found in the substance of the presacral nerve; with these some of the nerve fibres from the lumbar ganglia form synapses.

The presacral nerve dips into the pelvis, and about the level of the first part of the sacrum it divides into the two hypogastric nerves

From somewhere in the neighbourhood of this division, a large nerve passes on both sides to supply the lower part of each ureter. Each hypogastric nerve ends in a corresponding hypogastric ganglion, situated on a lateral aspect of the rectum (fig. 4); these ganglia may receive a few sympathetic fibres directly from the third and fourth sacral ganglia of the paravertebral sympathetic chains.

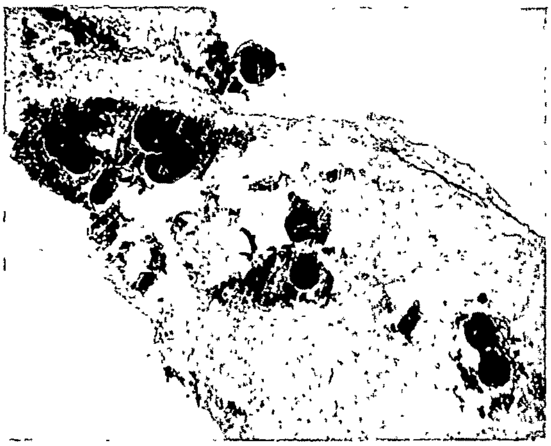

FIG. 3.—Section of presacral nerve, to show fasciculi lying in connective tissue. Stained for myelin in order to determine the numbers of preganglionic and postganglionic fibres present. (× 15, Weigert's myelin sheath stain.)

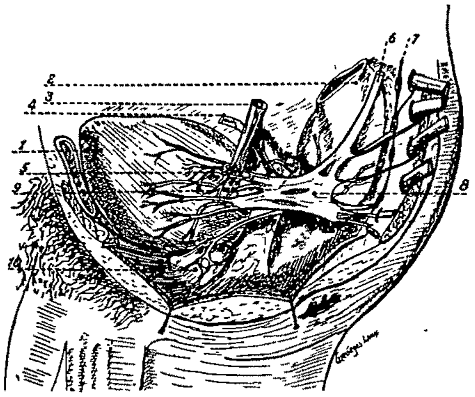

FIG. 4.—Left hypogastric ganglion, lateral aspect: *1*, bladder; *2*, rectum; *3*, ureter; *4*. vas deferens; *5*, vesical nerves; *6*, left hypogastric nerve; *7*, sacral sympathetic chain; *8*, hypogastric ganglion; *9*, seminal vesicle; *10*, prostate gland. The parasympathetic nerves from the second and third sacral nerves to the hypogastric ganglion are also shown. (After Laux.)

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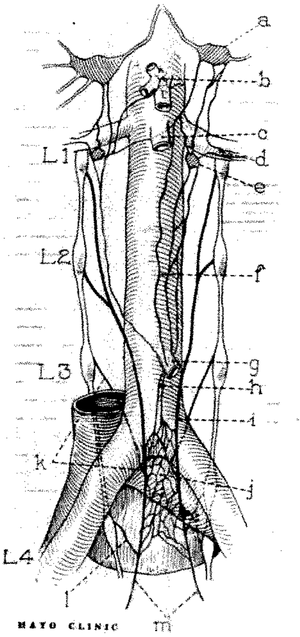

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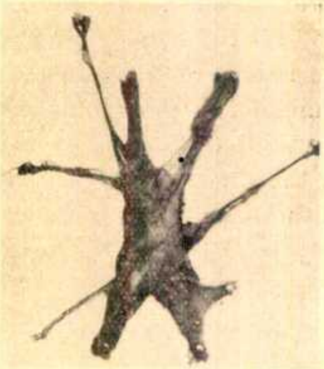

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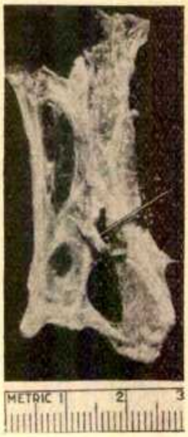
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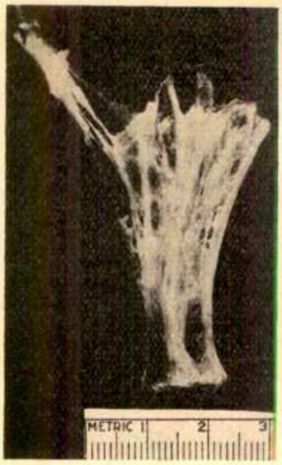
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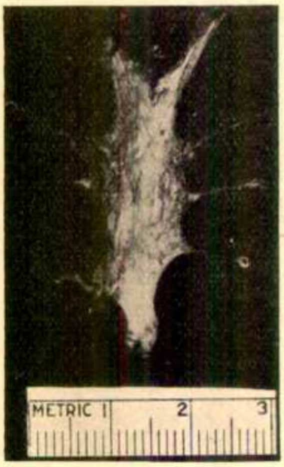
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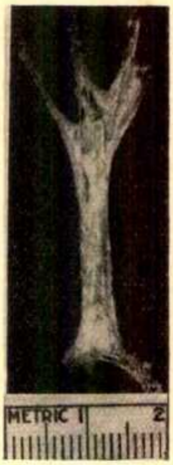
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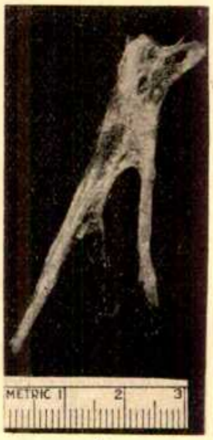
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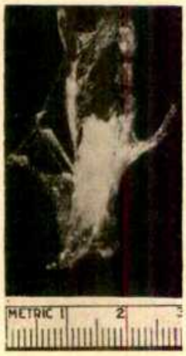
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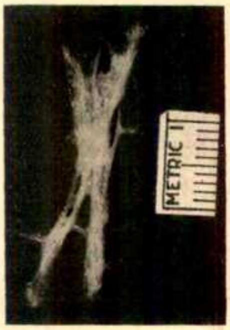
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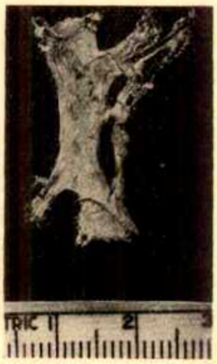
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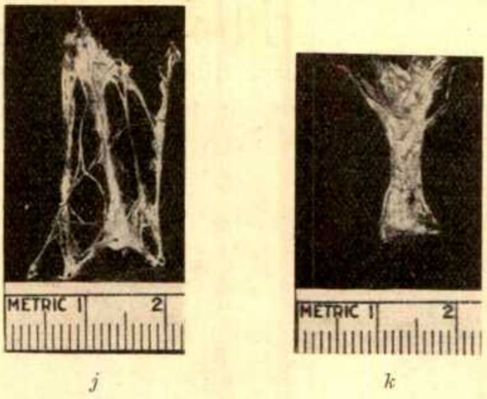

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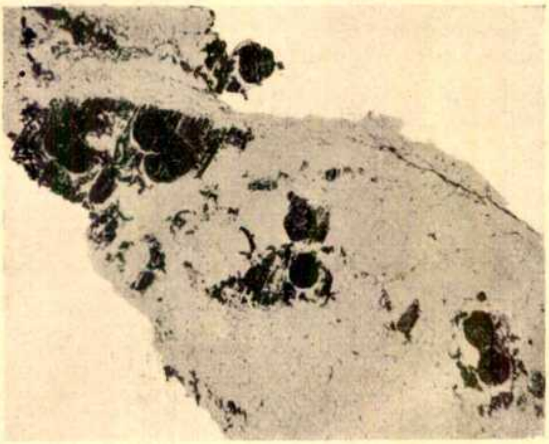

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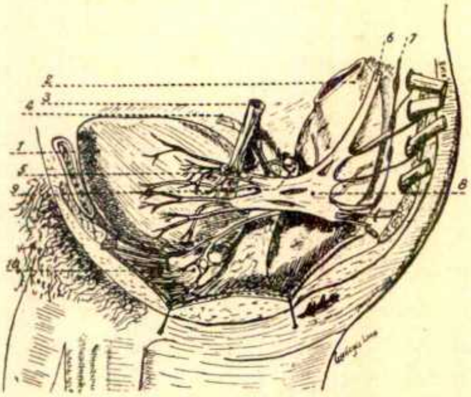

FIG. 4.—Left hypogastric ganglion, lateral aspect: *1*, bladder; *2*, rectum; *3*, ureter; *4*. vas deferens; *5*, vesical nerves; *6*, left hypogastric nerve; *7*, sacral sympathetic chain; *8*, hypogastric ganglion; *9*, seminal vesicle; *10*, prostate gland. The parasympathetic nerves from the second and third sacral nerves to the hypogastric ganglion are also shown. (After Laux.)

The parasympathetic nerves of the bladder are derived from the anterior primary divisions of the second and third sacral nerves on both sides (fig. 4). They join the corresponding hypogastric ganglia; there are no direct branches from the sacral nerves to the bladder. From the anterior borders of the hypogastric ganglia emerge a dozen or so branches of distribution, the upper branches containing both sympathetic and parasympathetic nerves for the bladder. The question of the situation of the synapses on these autonomic nerves will be considered later. The prostatic urethra and the external sphincter receive somatic fibres by way of the pudic nerves, which spring from the anterior primary divisions of the third and fourth sacral nerves; they do not pass through the hypogastric ganglia.

These intricate connections may now be examined in their broader physiological aspects. In the first place, it is necessary to dispose of the statement that the sympathetic nerves of the bladder are derived from a hypothetical inferior mesenteric ganglion, a mistake that has arisen from too slavish a transference of the arrangement in animals to conceptions of human physiology. It is true that in the human fœtus at the sixth week a definite inferior mesenteric ganglion has been described [6]. Such a structure is by no means constant in the adult; Petit-Dutaillis and Flandrin [16] identified it in five of thirteen subjects; Hovelacque [9] stated that it occurs in 50 per cent. of cases, and I myself have been able to identify it in but one of fourteen cases. Although it may be argued that lack of uniformity is a notorious feature of vesical innervation, and that when the ganglion is present it may play an important part in relaying the nerves to the bladder, on the other hand I shall show that important effects on the musculature of the bladder occur on stimulation of the lateral root of the presacral nerve. As the lateral roots are for the whole of their courses remote from the site of the supposed inferior mesenteric ganglion, I incline to the view that in man this structure has lost the physiological importance which it undoubtedly possesses in many other vertebrates. In the second place, it is well to emphasize the physiological fact that this nervous pathway contains direct connections between the nerves of the kidneys and those of the ureters and bladder. These connections ensure integration of the physiological processes concerned in the formation and the disposal of urine; they provide a pathway which probably co-ordinates the activity of the renal parenchyma, the transmission of urine along the muscular conduit formed by the renal pelvis and the ureter, the storing of urine in the bladder, and its final expulsion from that viscus.

PART II.—OBSERVATIONS ON THE INNERVATION OF THE BLADDER.

(I) *The exstrophic bladder.*—Before an opportunity of directly stimulating the vesical nerves occurred, I was able to settle one or two physiological points by making observations on exstrophic bladders. It may be objected that both the musculature and nerve supply of such a rudimentary bladder are likely to be abnormal; but the nature of the procedures was such that these objections have little weight.

(1) Effect of contraction of the interureteric muscle on the ureteral orifices.—In two cases of exstrophy of the bladder, I was able to produce strong contractions of the interureteric muscle by faradic stimulation. I found that the strongest obtainable contractions had no effect on the size or shape of the orifices of the ureters. Indeed, during such contractions it was possible to observe them opening for the expulsion of urine, and closing after the jet of fluid had ceased.

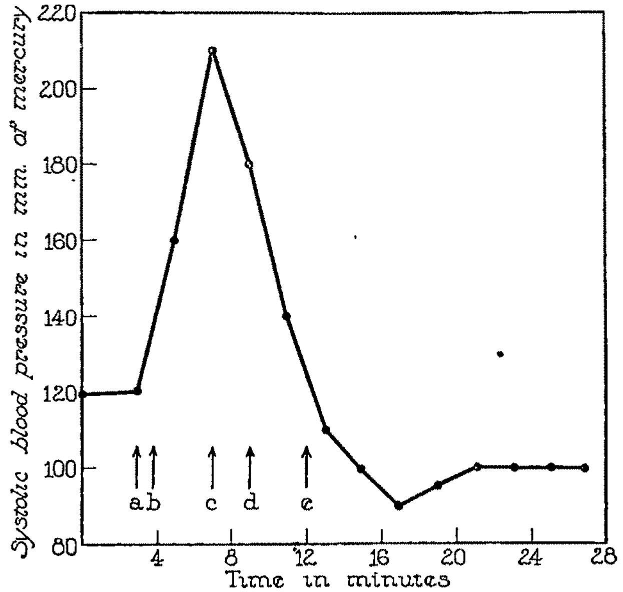

FIG. 5.—Effect of intravenous injection of adrenaline hydrochloride in a case of exstrophy of the bladder: (*a*) intravenous injection of 0·3 c.c. of 1 : 1000 adrenaline hydrochloride; (*b*) blanching and contraction of rudimentary bladder; (*c*) left ureteric orifice opened: four spurts of urine; (*d*) left ureteric orifice closed; (*e*) relaxation of rudimentary bladder.

(2) Effect of intravenous injection of adrenaline on the exstrophic bladder.—This was an attempt to determine the action of sympathetic nerves on the trigone and ureteric orifices of the bladder; these are the parts represented in the exstrophy. The patient was an adult, aged 24, whose right ureter had been transplanted to the bowel ten days pre-

viously. A dose was given of 0·3 c.c. of a 1 : 1000 solution of adrenaline hydrochloride, diluted in 5-c.c. of physiological saline solution. The blood-pressure was noted by means of a Pachon's self-recording oscillometer. The effect of the drug is shown in fig. 5. About thirty seconds after the blood-pressure began to rise, the rudiment of the bladder became contracted and blanched ; this appearance persisted for about eight minutes. Four minutes after the injection the left ureteric orifice, hitherto contracted, opened widely, and four spurts of urine appeared. After remaining open for two minutes the left ureteric orifice once more closed tightly. The right ureteric orifice remained closed throughout.

Thus the action of adrenaline was to cause contraction of the trigonal region, contraction of the ureteric orifice and increased expulsion of urine.

(II) *Results of faradic stimulation of the sympathetic nerve supply in the intact bladder.*—It has been possible to make direct observations on the nerve supply to the bladder on six occasions. Each of these operations was performed under spinal anæsthesia, which of course leads to paralysis of the sympathetic and parasympathetic fibres leaving the spinal cord as high as the sixth or seventh thoracic segment. Naturally, the paralysis is limited to preganglionic fibres, and the viscera are still under any controlling influences possessed by the peripheral ganglia, whether intrinsic or extrinsic. It may be thought that the use of spinal anæsthesia would obscure the factors to be investigated, but in actual practice difficulty was not encountered in interpreting the findings. Moreover, spinal anæsthesia does not lead to general dulling of nerve fibres and nerve cells throughout the body, as is the case with inhalation anæsthesia. The observations were made in such a way as to preclude the influence of any preconceived ideas; before beginning the research, I prepared a numbered table, showing the tests I desired to make on each part of the sympathetic nerve supply of the bladder.

Stimulation of:—

(1) Intact presacral nerve.
(2) Left hypogastric nerve.
(3) Right hypogastric nerve.
(4) Left lateral root.
(5) Right lateral root.
(6) Central end of cut presacral nerve.
(7) Central end of one cut hypogastric nerve, the other being intact.

When possible, each of these tests was carried out while observations were made on the orifices of the ureters, the trigone, the blood-vessels of the trigone, the internal sphincter of the bladder, the musculature of the prostate gland, and the musculature of the ejaculatory ducts. Each step was referred to by number only, and the observations made by the cystoscopist were recorded under that number; after the conclusion of the operation the results of each step were transferred to the procedure corresponding to the number. The cystoscopist was thus in entire ignorance of what was being done to the nerves.

Since the results obtained in all six cases were identical, I do not insert the protocol of each. The following description is a composite one. The current used was faradic, and the strength of stimulus was that which gave rise to a brisk twitch when the electrodes were applied to an exposed rectus abdominis muscle.

(1) The presacral nerve.—The effects noted were obtained whether the intact presacral nerve was stimulated, or the peripheral end of the divided nerve.

(*a*) Contraction of ureteric orifices. This contraction is a powerful one, the orifices assuming a pin-point appearance. Occasionally the contraction is preceded by the delivery of a forceful jet of urine. When the stimulus is discontinued, the orifices return slowly to the moderate degree of dilatation which is usual under spinal anæsthesia.

(*b*) Increased tonus in trigone. The term increased tonus is used advisedly, rather than contraction. The process appears to be a gradual tightening of the floor of the bladder, which disappears fairly rapidly when the stimulus is discontinued.

(*c*) Contraction of internal sphincter. This contraction has no appreciable latent interval. When the stimulus ceases, it may be about two minutes before the sphincter returns slowly to the moderately relaxed condition which is usual under spinal anæsthesia; however, it may relax at once. If an instrument is introduced through the sphincter, and the nerve is then stimulated, the instrument is grasped so tightly that considerable force is necessary to move it.

(*d*) Contraction of prostatic musculature. This is recognized by the cloud of prostatic secretion which is poured into the posterior urethra when the nerve is stimulated. Naturally it is less easily observed at each succeeding stimulus, as the prostatic glands are gradually emptied.

(*e*) Contraction of the musculature of the seminal vesicles and ejaculatory ducts. This is recognized by the forcible expulsion of semen into the posterior urethra. It is easiest to observe this at the first stimulation of the nerve.

(*f*) Contraction of the blood-vessels of the trigone. This is what might be expected, and is in keeping with the control of blood-vessels elsewhere. It is easy to recognize, since the vessels are previously somewhat relaxed by the action of the spinal anæsthetic.

(*g*) No observable effect on the musculature of the lateral walls and dome of the bladder. This is an important observation, as it sheds light on the mode of action of the inhibitory nerves which the presacral nerve will be shown to contain.

(2) Either hypogastric nerve.—Stimulation of the intact hypogastric nerve, or of its peripheral end after it had been severed from the presacral nerve, resulted in the following:—

(*a*) Contraction of the ureteric orifice on the same side. A contraction of the opposite ureteric orifice has never been noted.

(*b*) Tautening of the trigonal region. It has been impossible to decide whether this is an ipsolateral or a bilateral effect.

(*c*) Contraction of the internal sphincter.

(*d*) Contraction of the prostatic musculature.

(*e*) Contraction of the musculature of the seminal vesicles and ejaculatory ducts.

In short, the evidence at my disposal points to control of a ureteric orifice by the ipsolateral hypogastric nerve, while the internal sphincter and the musculature of the accessory generative organs appear to be affected as a whole by the stimulation of either hypogastric nerve.

(3) A lateral root of the presacral nerve:—

(*a*) Contraction of the internal sphincter.

(*b*) Contraction of the prostatic musculature.

(*c*) Contraction of the musculature of the seminal vesicles and ejaculatory ducts. I have not had an opportunity of observing the effect of stimulation of a lateral root on the ipsolateral ureteric orifice.

(4) Central end of cut presacral nerve. I have never been able to produce any observable reflex effect on the bladder by a stimulus, however strong, applied to the central end of the cut presacral nerve. The pain which is felt during the period of stimulation will be considered in a later section.

(5) Central end of one cut hypogastric nerve, the other being intact.—Effects on the bladder or internal sphincter have not been obtained, either before or after division of the presacral nerve. Thus I cannot present any evidence for the existence of a Sokownin reflex in man

(III) *The immediate results of division of the sympathetic nerves of the bladder.*—If the presacral nerve is cut above, the two hypogastric nerves below, and the intervening segment removed so as to free the bladder from all (or almost all) sympathetic influences, the following effects are observed:—

(1) The ureteric orifices, formerly slightly relaxed, become much more open.

(2) The entire trigone appears relaxed.

(3) The internal sphincter becomes much more relaxed.

(4) The blood-vessels of the trigone become widely dilated.

(5) There is no observable change in the dome and lateral walls of the bladder.

(IV) *The late results of division of the sympathetic nerves of the bladder.*—If the bladder is examined after the subject's convalescence, that is, about twenty-one days after the original operation, it will be found to have changed, so that its appearance is nearer the normal.

(1) The ureteric orifices now close in the intervals between each jet of urine.

(2) The trigone appears less relaxed, but still abnormal.

(3) The internal sphincter may close completely. However, it can be easily opened by the advancing beak of the cystoscope, and gives one the impression that it yields more rapidly than normally.

(4) The persistence of any marked degree of vascular dilatation in the trigonal region has not been noted.

TABLE I.—SUMMARY OF THE RESULTS OBTAINED BY STIMULATING THE COMPONENT PARTS OF THE PRESACRAL NERVE.

Structure	Nerve			
	Presacral	Hypogastric	Lateral root, presacral	Middle root, presacral
Ureteric orifice	Contraction	Contraction (ipsolateral)	Not done	Not done
Trigonal region	,,	Contraction	,,	,,
Internal sphincter	,,	,,	Contraction	,,
Prostatic musculature	,,	,,	,,	,,
Musculature of seminal vesicles and ejaculatory ducts	,,	,,	,,	,,
Blood-vessels of bladder	,,	Not done	Not done	,,
Dome and lateral walls of bladder	No effect	No effect	,,	,,

The significance of the foregoing observations will be considered in the next section. Here it may be emphasized that they furnish the first direct proof that the sympathetic system controls the trigonal region[1] and internal sphincter in the human being, as well as that they provide the first direct information regarding the innervation of the prostatic musculature and that of the seminal vesicles and ejaculatory ducts. I am conscious that there are deficiencies in the work, which are easily seen by reference to Table I. At an early stage I obtained indirect and collateral evidence which will enable me to offer a strong hypothesis in regard to the functions of the middle root of the presacral sympathetic nerve; therefore, as the opportunities for these investigations are few, I concentrated on obtaining accurate information on the functions of the other components of the nerve.

(V) *The effect of intravenous injection of adrenaline upon the capacity of the bladder.*—On two occasions I have endeavoured, during operation, to establish the presence of sympathetic inhibitory nerves to the vesical musculature by connecting the partially-filled bladder to a manometer and noting the effect of faradic stimulation of the presacral nerve on the intravesical pressure; but I found that a satisfactory technique was nearly impossible in the operating room. Although on both occasions a slight dilatation of the bladder appeared to follow sympathetic stimulation, I did not consider it conclusive, as in both cases the bladder was inflamed, and the increase in capacity not beyond the normal oscillations of pressure.

In order to settle this point, I determined to test the effect of intravenous injection of adrenaline on the capacity of a normally innervated healthy bladder. I myself was the subject of the experiment, the details of which follow. A catheter was introduced into the bladder and connected to a burette by a flexible rubber tube. On the burette was fixed a metric scale. The bladder was then filled with physiological saline solution, tinted with phenolsulphonephthalein, until there was a small head of fluid in the burette. This stage of filling was reached without any vesical discomfort, or any feeling that the bladder required to be emptied. A period of four minutes was then allowed to elapse, during which the level of the fluid in the burette remained constant, save for small respiratory excursions, which amounted to less than one unit volume. The adrenaline was then injected intravenously. To gauge the necessary dose, 0·2 c.c. of a 1 : 1000 solution of adrenaline hydrochloride was diluted with 3 c.c. of physiological saline solution; when 1 c.c. of this mixture had been injected (=0·07 c.c. of 1 : 1000 adrenaline hypochloride), the general effects of the drug became so marked that the injection was stopped. The results of the "chemical sympathetic" stimulation of the bladder are shown in figure 6. The observations of vesical capacity, which are, of course, relative, were made at intervals of twenty seconds, and if possible during expiration. The curve shows that there occurred an immediate active dilatation of the viscus, which remained at its new greater capacity for approximately five minutes. After this interval rhythmic oscillations in pressure appeared, although the mean pressure was maintained for approximately five and a half minutes at a lower level than at the beginning of the experiment. The experiment was terminated when a desire to void was felt.

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[1] Pharmacological evidence on this point has been published by Young and Macht [23].

These findings offer additional evidence that inhibitory fibres to the detrusor muscle of the bladder may be present in the human being.

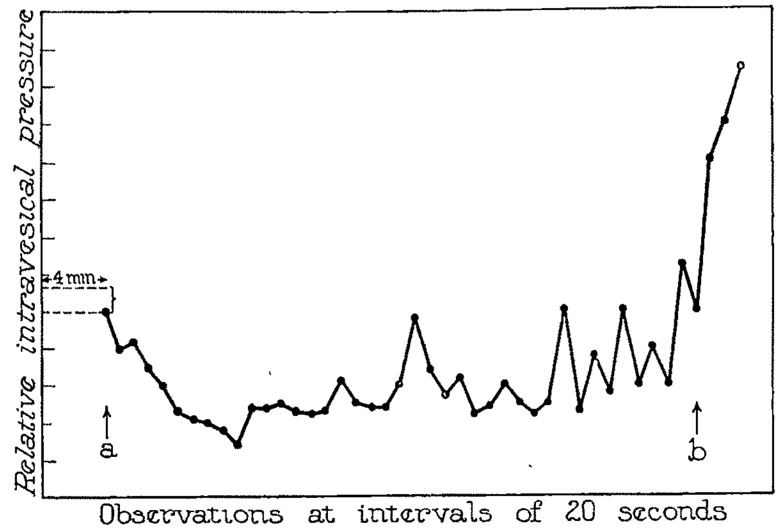

FIG. 6.—Effect of intravenous injection of adrenaline on the capacity of the bladder (*a*) injection of 0·07 c.c. adrenaline hydrochloride, 1 : 1000 diluted with 1 c.c. of physiological saline solution; (*b*) desire to void.

PART III.—ANALYSIS OF THE VARIOUS IMPULSES CARRIED BY THE NERVES OF THE BLADDER.

In this analysis of the paths followed by the various nervous impulses which reach or leave the bladder, I have made use of evidence from a number of sources. Some has been obtained directly during operations under spinal anæsthesia; the rest has been gathered from observations made after operation, from findings of post-operative cystoscopic examination, from examination of tissues in the post-mortem room, and from cases published by others—all these have contributed links from which it has been possible to construct a tolerably complete chain. In hominal research this method is almost the only one which can be used, for each problem is so complex that observations on one subject cannot be extended to cover the whole.

(I) *Afferent fibres.*—(1) Fibres which convey impulses which indicate the degree of distension (as distinguished from over-distension) of the bladder. I have elected to consider this aspect of vesical sensation first, because I regard it as the most important in the excitation of the micturition reflex. We have some information on this point from the report of Head and Riddoch [8]. One of their patients had had the lower end of his spinal cord destroyed by a wound. Therefore, the only remaining pathway from the bladder to the central nervous system was the sympathetic pathway, which entered the cord above the destroyed segments. Now this patient knew when his bladder filled up, although he was entirely unconscious of its emptying.

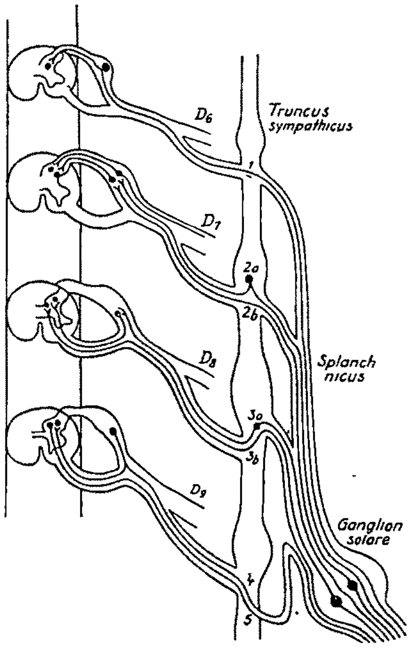

FIG. 7.—Paths by which an afferent fibre from a viscus may enter the central nervous system.

The sympathetic pathway contains fibres which convey impulses giving information as to the degree of distension of the musculature of the bladder.

On the other hand, in all the cases, fourteen in number, in which I have had occasion to resect the sympathetic pathway to the pelvic viscera, after operation distension of the bladder has been readily perceived by the patients. In these cases the only available pathway from the bladder to the central nervous system is by way of the pelvic (parasympathetic) pathway, and the second and third anterior primary divisions of the sacral nerves.

The parasympathetic pathway contains fibres which convey impulses giving information as to the degree of distension of the musculature of the bladder.

(2) Fibres which convey impulses of pain from the bladder.—I obtained my first accurate anatomical evidence on this point during the course of an operation, when I had occasion to grasp the presacral nerve (sympathetic pathway) with an artery forceps. When the nerve was pulled the patient complained of pain; after section of the nerve, traction on its central end caused pain. In this case, the effect of the spinal anæsthetic was passing off from above downward, although at the time the observations were made the skin was analgesic as high as the tenth thoracic segment. The impulses necessarily entered the spinal cord above this level, possibly along the roots of the splanchnic nerves. The description of the pain is interesting; it was characterized as "a crushing pain in my bladder." This is a remarkable example of the localization of visceral pain, and is in contrast with the statement of Head [7] that "the pain (of an overdistended bladder) is felt in the twelfth thoracic and first lumbar dermatomes." This patient, because of severe deafness, was quite unaware of the stage which the operation had reached, and thus the evidence is reliable. Even after leading questions he would not admit to feeling any such referred pain. During operation under light general anæsthesia, on several occasions I have seen patients show uneasiness when the central end of the cut presacral nerve was stimulated with a strong faradic current. I have much corroborative evidence from the statements of patients on whom section of the presacral nerve has been performed for painful conditions of the bladder; invariably the vesical pain has been diminished, although not abolished, by this procedure. It must be added, however, that there is no conclusive evidence regarding the stimulus which normally gives rise to such pain; probably, as is the case with other contractile viscera, it is either the overstretching or the spasmodic contraction of the muscle bundles which exercises a mechanical effect on the nerve fibres between them.

The sympathetic pathway contains afferent fibres which convey impulses set up by painful sensations in the bladder.

I have treated one patient, who had a painful condition of his bladder, by dividing the vesical branches of both hypogastric ganglia; thus the bladder was freed from all autonomic connections with the central nervous system. During the eight days in which he survived the operation he was entirely free from all forms of pain in the bladder. At the necropsy, I was able to satisfy myself that the neurectomy had been complete, and also to find an explanation for the pain around the neck of the bladder and in the posterior urethra, which had been part of his complaint. The prostate gland and posterior urethra had been invaded by a malignant growth. It must be concluded, therefore, that fibres using an autonomic pathway at least partly subserve sensation in the posterior urethra. This observation is contrary to the accepted view, which allocates the sensory nerve supply of the posterior urethra to the somatic fibres of the pudic nerve.

The parasympathetic pathway contains afferent fibres which convey impulses set up by painful sensations in the bladder. By this pathway also travel at least a proportion of the sensory nerves of the posterior urethra.

(3) Afferent fibres conveying impressions of tactile and thermal sensibility.—I can offer only indirect evidence regarding the path of the fibres which convey impressions of tactile and thermal sensibility. It is odd that the bladder should possess such fibres at all; however, they appear to be present, and to end especially around the three openings into the bladder [14]. Evidence of their presence in the sympathetic pathway could not be elicited by questioning the patient referred to on this page. On the other hand, it is of great interest that Riddoch's patient was able to tell when a catheter entered his bladder. In the cases in which the condition of the bladder allowed it to be done, estimation of the acuity of the tacto-thermal system after resection of the sympathetic pathway did not reveal any diminution in sensitivity.

The available evidence points to the view that almost all the afferent fibres conveying impressions of tactile and thermal sensibility traverse the parasympathetic system only; a few fibres of this nature, originating about the neck of the bladder, may travel by the sympathetic system.

(4) Afferent fibres concerned in the micturition reflex.—This is, perhaps, the best stage at which to consider the route followed by those

afferent fibres which subserve the micturition reflex; although logically the nature of adequate stimulus should be considered first. This point, as well as the sequence of events in the act, will be taken up later. It must be admitted that the only definite evidence on the question of the path traversed by "reflex" fibres is the fact that, after the first few days following resection of the sympathetic nerves of the normally innervated bladder, micturition is apparently normal. In a certain number of cases, the division of the inhibitory nerves which travel by the sympathetic pathway leads to some frequency; but this phase is transient, and although I have closely questioned the fourteen patients on whom I have performed this operation, I could not discover any evidence of departure from the normal, so far as micturition was concerned.

The sympathetic pathway from the bladder is not essential for the act of micturition. It follows as a corollary that by far the most important path for "reflex" fibres is the parasympathetic system, and ample evidence to support this view is forthcoming from various known diseases affecting the act of micturition, in which the lesion affects some part of the parasympathetic pathway. A detailed consideration of these would be out of place in this paper.

Most, if not all, "reflex" afferent fibres from the bladder reach the central nervous system by the parasympathetic pathway.

II.—*Efferent fibres.*—(1) Motor fibres to the detrusor muscles of the bladder.—So far as I am aware, all the information regarding the motor nerve supply of the detrusor muscle in the human being is derived from study of the effects of injury or disease upon the sacral segments of the spinal cord, the roots of the cauda equina, and the parasympathetic component of the second and third sacral nerves. It is a clinical fact, which need not be laboured in a paper of this nature, that destructive lesions of these parts of the nervous system lead to loss of ability to pass urine voluntarily, together with paresis of the muscular walls of the bladder which can be appreciated with the cystoscope. It is important to emphasize the word paresis used in the preceding sentence; that there is, in such cases, no complete or permanent paralysis of the intrinsic neuromuscular mechanism of the bladder is shown by the subsequent development of a more or less adequate "automatic bladder." Fibres springing from these parts of the central nervous system belong to the parasympathetic system. It has been shown that stimulation of the sympathetic pathway does not lead to any contraction of the detrusor muscle.

The parasympathetic nerves provide motor fibres for the detrusor muscle of the bladder.

(2) Motor fibres to the muscle guarding the uretero-vesical orifices.—I have already provided direct evidence that the ureteral orifices contract on stimulation of the vesical sympathetic nerves.

(3) Motor fibres for the trigonal muscle.—As I have shown, the sympathetic pathway provides motor fibres for the trigonal muscle.

(4) Motor fibres for the internal sphincter of the bladder.—I have shown that the sympathetic pathway provides motor fibres for the internal sphincter of the bladder.

(5) Inhibitory fibres for the detrusor muscle.—Although Elliott [3] has stated that there are no inhibitory nerves to the detrusor of the bladder in the human being, I shall present evidence which appears to put their existence beyond doubt.

(*a*) In the first place, all surgeons interested in this field are aware of the transitory period of frequency of micturition which occasionally follows division of the sympathetic nerves of the bladder. It may be objected that the frequency passes off, so that in a few days no change from the normal can be detected. This objection is reasonable, but by no means insuperable. Many examples are known in which an intact part of the central nervous system takes over the function of a part which has been destroyed.

(*b*) In the second place, I have had the opportunity of following, for one year and for eight months respectively, two cases in which the most reasonable explanation of the operative cure of vesical paralysis is the assumption that the sympathetic nerves of the bladder contain a proportion of inhibitory fibres.

The first of these patients [13] was ideal for the investigation of this physiological problem, because the damage to his central nervous system was easy to define. Briefly, he showed evidence of damage to the second, third, fourth, and fifth sacral segments of the spinal cord, that is, to the segments from which the parasympathetic nerves to the bladder take their origin. He was able to micturate only with great difficulty, and so incomplete was the act that his bladder contained on an average about 300 c.c. of residual urine. There was, therefore, a pure picture of the pathological physiology of the bladder when its parasympathetic supply is greatly reduced, while its sympathetic supply is intact. To correct this imbalance, it seemed justifiable to divide the sympathetic nerves to the bladder, on the hypothesis that they might, through their inhibitory fibres, "over-brake" the efforts of the detrusor to expel urine. This was accordingly done. The result of the operation was immediate; after his convalescence the patient was able to empty his bladder completely, and when he was examined again, a year after the operation, his cure was maintained.

The second case also was excellent for physiological purposes. A child aged 8 had suffered, at the age of 3 years, from a form of paralysis which affected his lower extremities and his bladder. The highest affected segment of the spinal cord was therefore the second lumbar. Although the paralysis of the legs disappeared, that of the bladder persisted, and when I saw him he had been catheterized three times a day for five years. It seemed to me that here again an intact sympathetic pathway was acting as too effective a restraint upon the activity of the parasympathetic pathway, and that the imbalance might be corrected by division of the sympathetic nerves of the bladder. Happily this proved to be the case, and since the sympathectomy the child has been able completely to empty his bladder.

(*c*) The effect of intravenous injection of adrenaline provides additional evidence.

All available evidence points to the hypothesis that the sympathetic nerves of the bladder provide inhibitory fibres to its detrusor muscle.

(6) Inhibitory fibres to the internal sphincter.—Although it is possible that a few inhibitory fibres pass with its motor fibres in the sympathetic pathway, there is no doubt that the majority reach the internal sphincter by way of the parasympathetic nerves. The best proof of this contention lies in the apparently normal way in which micturition can be carried out after sympathectomy has been performed on a previously normally innervated bladder. The physiology of the internal sphincter will be considered in more detail in a later section.

(7) Vasoconstrictor fibres to the vesical arteries.—I have already pointed out that a certain degree of vasodilatation of the vesical arteries is to be expected as a result of spinal anæsthesia. This is an advantage because the constriction of the vessels, which occurs when the sympathetic pathway is stimulated, is more easily observed. The temporary increase in vasodilatation which follows section of the sympathetic pathway is of much interest; as will be shown, it provides a clue to the nature and origin of that component of the sympathetic pathway which controls tonus in the walls of the vessels.

The sympathetic pathway contains vasoconstrictor fibres for the vesical blood-vessels.

III.—*The segmental levels of the spinal cord associated with the innervation of the bladder.*—(1) Parasympathetic fibres.—There appears to be some variability in the path of the parasympathetic nerves to the spinal cord. Usually they are connected chiefly with the second and third sacral nerves. The branches from the third sacral nerve seem to be constant; those from the second sacral nerve are less constant, and, indeed, Latarjet and Bonnet [10], who speak with authority on the pelvic autonomic system, have never seen branches arising from this nerve. Not infrequently some parasympathetic fibres arise from the fourth sacral nerve; and in an isolated case examined by Cordier [2] there was such a branch from the first sacral nerve.

The second and third sacral are the most important spinal segments connected with the parasympathetic pathway to the bladder.

(2) Sympathetic fibres.—Knowledge of the levels at which vesical sympathetic fibres enter and leave the spinal cord is far from complete. This is largely the result of the intricacy of the connections of the whole thoracico-abdominal sympathetic system, together with the fact that the physiological method of degenerative section of the various nerves is not applicable to man. There are, however, certain points of departure which may be used in studying this aspect of vesical physiology. (*a*) It is known that the whole efferent thoracicolumbar sympathetic system is connected to the spinal cord between the first thoracic and second lumbar spinal segments, inclusive. (*b*) Afferent splanchnic fibres are not limited to this extent of the spinal cord, but may enter it by the anterior or posterior roots of any segment. Foerster's [4] diagram (fig. 7) shows the routes open to such a fibre. (I am not concerned, in this paper, with the relative merits of the "purely efferent" and the "efferent-and-afferent" conceptions of the sympathetic system.)

(*a*) Efferent fibres.—There is no precise evidence available to indicate the segments of the spinal cord which provide motor and inhibitory fibres for the bladder. So far as the skin of the trunk is concerned, it has been shown by Thomas [19], with the aid of the pilomotor reflex, that its sympathetic fibres are derived from the eighth and ninth thoracic segments. On the other hand, the highest roots of the splanchnic nerves are derived from the fifth thoracic sympathetic ganglia, although this level does not necessarily correspond to the spinal level of the preganglionic fibres concerned. If Thomas's conclusions be accepted, it is unlikely that there is a close relationship between the sympathetic innervation of the dermatomes and that of the viscera; but that two spinal segments supply sympathetic fibres for eleven dermatomes (second to twelfth thoracic) is at least open to doubt.

An accurate origin of the efferent sympathetic fibres to the bladder cannot be given.

(*b*) Afferent fibres.—Some notion of the central connections of the afferent sympathetic fibres to the bladder can be gathered by correlating various scattered observations. It was observed by Head and Riddoch that in cases of total transverse interruption of the spinal cord below the level of the tenth thoracic segment, the passage of a catheter was perceived at the neck of the bladder, and that the patients knew when the bladder was distended. I have already stated that I have been able to produce sensations of pain referred to the bladder by stimulating the sympathetic pathway, when there was analgesia of the skin as high as the tenth thoracic segment. These two observations are complementary. Foerster stated that the afferent sympathetic fibres of the hypogastric nerves reach the spinal cord through the eleventh and twelfth thoracic, and the first, second and third lumbar spinal roots; in the light of my own experience, they must make central connections as high as the ninth thoracic segment. Pieri [17] has attacked the problem by anæsthetizing the spinal roots in turn, until he secured amelioration of vesical pain; he inclines to the view that the third and fourth lumbar roots transmit the majority of the sensory nerves of the bladder, but adds "mes idées là-dessus ne sont pas encore fixées avec certitude." I have had the privilege of discussing this matter with Professor Pieri (December, 1930): he told me he was still uncertain with regard to this point.

Afferent fibres traversing the sympathetic system reach the spinal cord at least as high as the ninth thoracic segment, and probably as low as the fourth lumbar segment.

(3) Somatic fibres.—(*a*) The somatic motor fibres for the external sphincter of the bladder reach the muscle from the third and fourth sacral segments, through the pudic nerve. (*b*) The exact part played by the sensory fibres of the pudic nerve (third and fourth sacral segments) in the innervation of the posterior urethra is doubtful. I have submitted evidence that the major part of the sensory nerve supply of this part of the urethra is by autonomic fibres, through the hypogastric ganglia. Judging from the area to which pain is referred in lesions of the prostatic urethra, these fibres are most likely to be parasympathetic; they would thus enter the cord chiefly by the second and third sacral roots.

PART IV.—THE PHYSIOLOGY OF THE COMPONENT PARTS OF THE BLADDER.

(I) *The detrusor muscle.*—It has been seen that the "detrusor" muscle receives motor fibres from the parasympathetic system, and inhibitory fibres from the sympathetic system. There is no evidence that contraction of the detrusor can be initiated or continued by the direct action of the will. With regard to the inhibitory fibres the position is not nearly so clear, and it will be necessary, at this point, to examine briefly the nature of inhibition in the urinary bladder of the human being. Broadly speaking there are two ways in which these fibres may function. Either they may carry impulses which "unlock" the tonus of the muscle fibres, so that the bladder may be passively dilated to a greater capacity, or they may act as a brake on the force and completeness of the expulsive efforts of the bladder as a whole. The effect of intravenous injection of adrenaline on the capacity of a normal bladder appears to show that fibres are present which function in the first way. In this instance the plastic tonus of the bladder had come into equilibrium with a constant head of fluid; sympathetic stimulation so reduced the tonus as to permit the entrance of a further quantity of fluid. Moreover, for a certain period the plastic tonus of the bladder remained in equilibrium with this increased amount of fluid, though the "head" of fluid in the reservoir, and therefore the fluid pressure exerted on the walls of the bladder, became notably less. Finally, the desire to void made its appearance rather suddenly, at the end of a slow rise of intracystic pressure, although this pressure was at the time notably lower than that exerted by the "head" of fluid at the beginning of the experiment. It may be deduced that sympathetic activity is sufficient to adapt the length of the muscle fibres to accommodate more fluid, although the fluid is offered to the viscus at the same pressure as or even at a lower pressure than, that of the fluid with which the musculature was originally in equilibrium.

On the other hand, the results of sympathetic neurectomy in the two cases cited, in which inability to empty the bladder resulted from functional impairment of the parasympathetic system, the sympathetic system remaining intact, seem to me almost to force acceptance of the hypothesis that sympathetic influences act as a brake on contractions of the detrusor. Furthermore, they must act as a continuous brake, and not merely as a bar to initiation of the contraction of the muscle. Otherwise, the difficulty would lie merely in beginning the flow, and once started the muscle would be able to empty the bladder.

There is here a mechanism the voluntary putting into action of which might be one available method of checking the usual response to the desire to micturate.

There remains to be explained the method by which the bladder accommodates itself to contain a normal amount of urine, after the operation of sympathetic neurectomy. That there is often a definite period required for this accommodation may be judged from the transient frequency of micturition which may follow the neurectomy. Moreover, normal capacity cannot result from passive over-stretching of desympathectomized muscle fibres, for this would be a process limited only by the non-vital factor of limit of stretch, and the last state of the patients would be worse than the first, whereas they have remained cured. Therefore, there must be assigned to the muscle fibre and to the parasympathetic system the ability to acquaint higher nerve centres with the degree of tension under which they find themselves.

(II) *The ureteric orifices.*—Although stimulation of the sympathetic nerves of the bladder leads to simultaneous contraction of both trigone and ureteric orifices, it must, I think, be admitted that the control of these two structures may be dissociated to a certain extent. The evidence for this hypothesis is based on my observation that after the intravenous administration of adrenaline the orifices may open although the trigone is contracted. This evidence is not unassailable, inasmuch as the subject of the experiment is necessarily suffering from an anatomic deformity; moreover, it may be that the orifices are passively opened by the active flow of urine. To clarify the problem it would be essential to secure a number of observations correlating the occurrence of the waves of contraction and dilatation which normally pass over the filling bladder with the opening and closing of the orifices. At present it is not known whether the trigonal musculature participates in these contractions. If there is a neuro-muscular mechanism which arranges that the ureteric orifices be closed when the bladder is contracting, it must also arrange for the ordered delivery of urine from the renal pelvis to the bladder, and the existence of a sufficiently connected nervous network to undertake this work has been described. In addition, the oblique manner in which the terminal part of the ureters enters the bladder tends to prevent reflux up the ureters at each vesical contraction.

(III) *The internal sphincter.*—It has been shown in the preceding parts of this paper that stimulation of the sympathetic nerves of the bladder gives rise to contraction of the internal sphincter. The ability of the sphincter to remain closed after sympathetic neurectomy proves that it must also possess an inherent tonus of its own. On the other hand, it is a urological commonplace that in so-called "cord bladder" the internal sphincter is found to be relaxed; in these cases the lesion is situated somewhere in the parasympathetic pathway. We are forced to conclude that maintenance of closure of the internal vesical sphincter depends upon its inherent tonus, which in turn depends upon the integrity of reflex fibres in the parasympathetic pathway; and that its sympathetic supply merely reinforces this closure. With regard to the actual closure of the sphincter, after it has been opened, there are two possibilities. The first is that this is initiated by sympathetic nerves; the second is that closure is due to the cessation of inhibitory influences reaching it along parasympathetic fibres. The fact that in the female incontinence does not follow the operation of sympathetic neurectomy disposes of the first hypothesis; for in this sex the external vesical sphincter has little if any independent control of the urinary bladder. It may be concluded, therefore, that closure of the sphincter is due to its own tonic contraction when inhibitory influences cease to reach it. Since it is possible for a woman to interrupt the flow of urine after sympathetic neurectomy, it follows as a corollary that here is one incontrovertible proof that the will can be exerted through the medium of the autonomic nervous system.

With regard to the mechanism of the opening of the sphincter, there are two existing hypotheses. The first is that its tonus is directly relaxed by inhibitory influences passing over parasympathetic nerves; the second, suggested by Young and Davis [22], is that it is opened mechanically by the pull of extensions of the trigonal musculature, which pass within the grasp of the sphincter to insertions in the posterior urethra. As I have shown, stimulation of the sympathetic pathway leads to contraction of both trigone and internal sphincter; contraction of the trigone has not been observed to open the sphincter. It may be concluded that the opening of the internal sphincter is due to inhibition of its natural tonus; it is obvious that it is possible to accomplish this by the exercise of the will, for example, in voluntary micturition.

In both these respects my observations confirm the original work of Rehfisch [18] on the voluntary control of the internal sphincter.

(IV) *The blood-vessels of the bladder.*—Spinal anæsthesia naturally leads to vaso-dilatation in the structures anæsthetized. It was, therefore, to be expected that the vessels of the bladder would be noticeably dilated during my operations. It was found that the dilatation became notably more pronounced on division of the sympathetic nerves. At first this was a little surprising. In seeking its explanation, I remembered that it had been shown by Adson [1] that complete vaso-dilatation of the vessels of the extremities could be secured only if all the rami communicantes to the limb were divided, and that interruption of the preganglionic fibres was insufficient. Obviously, then, postganglionic vasomotor fibres were interrupted by division of the presacral nerve. Histologically these pass in the middle root. I am inclined to believe, therefore, that the majority of fibres of the presacral nerve which are derived from the intermesenteric plexuses are vasomotor in nature.

(V) *Sensation in the bladder.*—It has been seen that afferent fibres subserving sensation are present in both the sympathetic and the parasympathetic vesical nerves. As a result of my experience with neurectomy of these nerves, it has been possible to determine with a tolerable degree of certainty the paths pursued by the fibres subserving different types of sensation. Parts of the mucous membrane of the bladder are sensitive to touch as well as to painful stimuli. In addition, like all other hollow viscera, its over-distension and its disordered or spasmodic contraction give rise to painful sensations by stretching or squeezing its intramural nervous network. Now it has been an invariable finding after sympathetic neurectomy that relief is obtained from the pain of spasmodic contraction; on the other hand, the most careful examinations have not detected any diminution in the sensitivity of the mucous membrane to tactile or to painful stimuli. Therefore I incline to the view that fibres subserving the latter types of sensation pursue an exclusive parasympathetic route, whereas fibres subserving the former types travel largely by the sympathetic pathway.

(VI) *Afferent fibres for the micturition reflex.*—I have pointed out that after sympathetic neurectomy micturition is normal, so far as it is possible to determine. It has been held by some that the pudic nerves supply a proportion of reflex fibres, on account of their hypothetical sensory distribution to the posterior urethra. I have shown that it is probable that the sensation of the posterior urethra depends on fibres reaching it along autonomic routes; moreover, it has been shown repeatedly that after the operation of bilateral pudic neurectomy [12, 21], the act of passing urine can be carried out in a normal manner. From a physiological standpoint, therefore, it may be concluded that only the parasympathetic pathway is essential for the act of micturition.

PART V.—THE ACT OF MICTURITION.

Of late years the settling of many debated neurophysiological matters has clarified discussion of the physiology of the act of micturition. Among these may be mentioned the possibility that the will could be exercised by way of autonomic nerves, and the tendency to regard the posterior urethra or the external sphincter as the "trigger zone" for starting the act. Reluctance to accept the former obscured the true explanation of voluntary micturition. The latter hypothesis, revived by Müller in 1918, was an attempt to dispense with the former by substituting an alternative explanation which would be acceptable to current physiological thought.

It seems to me that the simplest way to regard the act of micturition is as a modified autonomic reflex, which may be set in motion and completed by a stimulus applied at one of two points. These reflex "triggers" are the vesical musculature, for which the adequate stimulus is the degree of distension of the viscus, and the internal vesical sphincter. When the adequate stimulus is applied to the first the opening of the internal sphincter is arranged for automatically; this is the mechanism of micturition on desire to urinate. On the other hand, when the internal sphincter is voluntarily relaxed the detrusor muscle automatically contracts; this is the mechanism of voluntary micturition.

It may be urged, reasonably enough, that the term "reflex" is hardly applicable to a process which may be voluntarily interrupted at any point in the cycle. It is true that, in the male at least, there is a possibility that the interruption may be due to the presentation of an insuperable barrier to the outflow of urine by the voluntary closure of the external vesical sphincter. Personal experiment is sufficient to dispose of this hypothesis; for it will be found that sudden interruption of the urinary stream is not followed by a feeling as if the bladder were trying to overcome an obstruction at its outlet. In other words, as the internal vesical sphincter is closed, there is a simultaneous stopping of the contraction of the detrusor muscle, which at once assumes a plastic tonus commensurate with the vesical content at the time. It is also a matter of surgical experience that the urinary flow can be interrupted with a similar lack of discomfort after the operation of prostatectomy, when, owing to the surgical destruction of the internal sphincter, only the external sphincter is available to check the stream. Either the change in the behaviour of the detrusor muscle is the result of a reflex, whose afferent paths may begin either in the internal sphincter (autonomic segment of arc) or in the external sphincter (somatic segment of arc), or the neural impulses necessary for interrupting the stream are integrated at a higher level, and flow from this level simultaneously to sphincter and detrusor. Obviously the latter hypothesis is the more attractive; and since it has been shown that the parasympathetic is the only peripheral pathway essential for voluntary interruption of the flow, it may be added as a corollary that the integrating centre is situated in the second, third and possibly the fourth sacral spinal segments. If this view be accepted, the conception of micturition as a pure reflex must be limited to infancy, and the gradual development of adult control must be ascribed to the more and more complete subjugation of an originally primitive spinal function to cerebral influences. It is hardly necessary to add that many analogous processes could be mentioned. Be that as it may, there is still to be explained the presence of an adequate external sphincter in the male; in the female it is generally agreed that this structure is so unimportant that it may be discounted in considering the normal physiology of the organ. I must confess that at present no adequate teleological explanation is available.

The term "reflex," then, may be applied correctly to the act of micturition in infants; and it may also be applied to the process of automatic micturition which may follow interruption of the spinal cord at any level compatible with life. It is a fact of supreme physiological importance that the manner in which the bladder empties itself, after the establishment of automatic micturition, is the same at whatever level the cord is injured [20]. The presence of extraspinal reflex centres of sufficient complexity to complete the act must therefore be conceded. The next step is to ascertain the locality of these centres, and this at once raises the question, at what points on their pathway parasympathetic and sympathetic fibres are interrupted by synapses.

It has been shown that approximately 40 per cent. of the fibres of the presacral nerve are postganglionic, and I have advanced the hypothesis that these are vasomotor fibres whose cell stations are situated in the great visceral ganglia and in the scattered ganglion cells which are found in the plexuses about the aorta, and even in the presacral nerve itself. The remainder of the sympathetic fibres, and the parasympathetic fibres, must be interrupted either in the hypogastric ganglia or in the vesical ganglia on the walls of the viscus. If these fibres follow the general morphological rule for autonomic nerves, the sympathetic fibres would be interrupted in the hypogastric ganglia, with the possible exception of those for the internal vesical sphincter, which, as Gaskell [5] pointed out, tend to have their synapses in or near the structure which they innervate. On the other hand, the parasympathetic fibres would pass through the hypogastric ganglia, to be interrupted in the vesical ganglionic plexuses. An opportunity for settling these points histologically has not as yet presented itself; but the matter will be investigated if and when a suitable case comes to necropsy.

NOTE ON THE INNERVATION OF CERTAIN MALE GENITAL ORGANS.

In the course of my research upon the innervation of the bladder, various points of interest in the innervation of the male genitalia have been brought to light. It has been shown that stimulation of the sympathetic nerves to the pelvis leads to expulsion of semen from the ejaculatory ducts, as a result of contraction of the musculature of the seminal vesicles, and to expulsion of secretion from the prostatic ducts, as a result of contraction of the unstriped musculature which permeates the gland. It is of great physiological interest that, following sympathetic neurectomy, male patients have found that although they could perform the sexual act, and although they experienced a psychical orgasm indistinguishable from the normal, ejaculation did not occur. Now it is known that after the operation of lumbar sympathectomy, in which the second, third, and fourth lumbar ganglia, together with the intervening trunks, are removed, there is no such alteration of sexual function. By a process of exclusion, it is obvious that the motor fibres for the vesicles and efferent ducts must reach the presacral nerve either in the branches which it receives from the first lumbar ganglia or in its middle root. I have presented evidence which makes it probable that the middle root has a vasomotor distribution; it would appear, therefore, that the motor fibres in question pass in the branches from the first lumbar ganglia to the lateral roots of the presacral nerve. It may also be concluded that the sensations constituting the orgasm are not directly associated with contractions of the musculature of the seminal vesicles and ejaculatory ducts.

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THE COMPONENT REFLEXES OF MICTURITION IN THE CAT.

PARTS I AND II.

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FIVE component reflexes of micturition in the cat have been described [Guyon, 1900], [Barrington, 1914], namely:—

(1) A hind-brain reflex evoked by distending the bladder, effecting a contraction of the bladder and having both its afferent and efferent paths in the pelvic nerves.

(2) A hind-brain reflex evoked by running water through the urethra, effecting a contraction of the bladder and having its afferent path in the pudic and its efferent in the pelvic nerves.

(3) A spinal reflex evoked by distending the proximal urethra, effecting a slight, transitory contraction of the bladder and having both its afferent and efferent paths in the hypogastric nerves.

(4) A spinal reflex evoked by running water through the urethra, effecting relaxation of the urethra and having both its afferent and efferent paths in the pudic nerves.

(5) A spinal reflex evoked by distending the bladder, effecting a relaxation of the urethra and having its afferent path in the pelvic and its efferent in the pudic nerves.

PART I.

If the five reflexes mentioned were the only ones existing, division of the pelvic nerves in a cat, in which the spinal cord, near the level of the last rib, and the pudic nerves had previously been divided, would not produce any increase in the volume of residual urine. The following four experiments show that in fact such an increase does occur. Experiment 4 shows further that this increase is a result of division of nerve fibres and not of some other lesion made at the operation.

(1) Female. Pudic nerves divided, and five to six weeks later the spinal cord transected in the last thoracic and first lumbar segments.

6th day	Residual urine	115 + (5) c.c.	
14th ,,	,, ,,	120 + (10) c.c.	
20th ,,	,, ,,	90 c.c or less.	
25th ,,	,, ,,	60 c.c. or less.	
29th ,,	,, ,,	70 c.c.	
33rd ,,	,, ,,	65 c.c.	
41st ,,	,, ,,	80 c.c.	Pelvic nerves divided.
45th ,,	,, ,,	170 c.c.	(Hæmaturia.)
49th ,,	,, ,,	250 c.c.	
54th ,,	,, ,,	285 c.c.	(Cystitis.)

(2) Castrated male. Pudic nerves divided and spinal cord transected in the last thoracic and first lumbar segments.

4th day	Residual urine	135 + (40) c.c.	
9th ,,	,, ,,	185 c.c.	
17th ,,	,, ,,	45 c.c.	
25th ,,	,, ,,	120 c.c.	
30th ,,	,, ,,	50 c.c.	
37th ,,	,, ,,	90 c.c.	
40th ,,	,, ,,	75 c.c. or less.	Pelvic nerves divided.
46th ,,	,, ,,	195 c.c.	
51st ,,	,, ,,	205 c.c.	
54th ,,	,, ,,	175 c.c. + (25) c.c.	

(3) Female. Pudic nerves divided and spinal cord transected in the last thoracic segment.

3rd day	Residual urine	110 c.c. + (an unknown volume) or less.	
8th ,,	,, ,,	100 c.c. + (10) c.c. or less.	
11th ,,	,, ,,	215 c.c. + (10) c.c.	
13th ,,	,, ,,	125 c.c. + (50) c.c.	
17th ,,	,, ,,	120 c.c. + (10) c.c.	
19th ,,	,, ,,	125 c.c.	
21st ,,	,, ,,	140 c.c. or less.	
25th ,,	,, ,,	80 c.c.	
29th ,,	,, ,,	110 c.c.	
32nd ,,	,, ,,	170 c.c.	Pelvic nerves divided.
37th ,,	,, ,,	225 c.c.	
42nd ,,	,, ,,	220 c.c.	
47th ,,	,, ,,	175 c.c.	
51st ,,	,, ,,	115 c.c. (Hæmaturia).	
56th ,,	,, ,,	125 c.c. or less (Hæmaturia).	
59th ,,	,, ,,	160 c.c. (Hæmaturia).	
63rd ,,	,, ,,	85 c.c.	
67th ,,	,, ,,	85 c.c. + (20) c.c. or less.	
71st ,,	,, ,,	130 c.c.	
78th ,,	,, ,,	55 c.c.	
80th ,,	,, ,,	40 c.c.	
88th ,,	,, ,,	85 c.c.	
94th ,,	,, ,,	35 c.c.	
99th ,,	,, ,,	110 c.c.	
101st ,,	,, ,,	85 c.c.	

(4) Female. Inferior mesenteric ganglia excised and spinal cord transected in the last thoracic segment. Fifty-one days later the pudic nerves were divided.

6th day	Residual urine	12 c.c.	
9th ,,	,, ,,	15 c.c.	
10th ,,	,, ,,	10 c.c.	
12th ,,	,, ,,	7 c.c.	sacral spinal roots divided.
14th ,,	,, ,,	50 c.c.	
16th ,,	,, ,,	85 c.c.	
18th ,,	,, ,,	130 c.c.	
24th ,,	,, ,,	155 c.c.	
31st ,,	,, ,,	75 c.c.	
37th ,,	,, ,,	45 c.c.	

In the above descriptions, when a residual urine is stated to be a certain volume "or less," it means that such a volume was obtained by emptying the bladder by expression, but that it was not known that the last previous passage of urine was so short a time before that the volume secreted in the interval was negligible. When a second figure in brackets is given after a + it means that the first volume was measured and that some urine was still left in the bladder the volume of which was estimated, from the size the bladder felt, to be that in the brackets.

Therefore, there must exist a spinal reflex, or reflexes, having both paths in the pelvic nerves and effecting a relaxation of the urethra, or a contraction of the bladder, or both. In the four experiments just described it was not obvious from the feel of the bladder, when it was being expressed, that the resistance of the urethra was increased after division of the pelvic nerves.

An attempt to obtain direct evidence of such reflex relaxation of the urethra was made in the following way. Female cats only were used. The cat was anæsthetized with chloroform, a spinal transection made about the level of the last rib and both pudic and both hypogastric nerves were divided. The pelvic nerves were then freed and a thread put loosely round each. The cat was then decerebrated, the administration of chloroform stopped, and at least half an hour allowed to elapse before going on with the experiment. A brass catheter was then passed and the bladder emptied. The catheters used were numbers 5 and 7 (Charrière), i.e., $\frac{5}{3}$ and $\frac{7}{3}$ millimetres in diameter; size 5 appeared the better. The catheter was then connected with a graduated, warm water reservoir fitted with a clamp and capable of being raised and lowered to given heights, to alter the pressure of the water at the catheter when the clamp was open. A given height of the water above the catheter being kept constant, the water was allowed to run in the catheter until the volume run in did not increase. The height was then increased a known amount and the same process repeated until water was seen to escape from the urethra alongside the catheter, and the pressures when this just did not and just did occur were noted. In this way no clear results were obtained because there was a continual rise in the bladder volume for each given intravesical pressure and a continual rise in the intravesical pressure necessary to cause escape of water from the urethra, as successive observations were made, before division of the pelvic nerves.

A second set of experiments were made in the same way except that the transection was made, with or without the division of the pudic or hypogastric nerves or of both, and an interval of two weeks or more allowed to elapse before isolating the pelvic nerves, dividing the pairs of nerves remaining, and decerebrating the cat. The experiments were then proceeded with as before. In them, as in other experiments where an interval was allowed to elapse between the nerve division and the final operation, the inferior mesenteric ganglia were excised at the time of division of the hypogastric nerves and 1 to 2 cm. of the pudic nerve excised at the time of its division. The results are shown in the following table.

Interval, in days, between the spinal transection and the decerebration	Nerves divided at the time of the transection	Minimum intravesical pressure, in centimetres of water, which lead to the escape of water from the urethra	
		Before division of the pelvic nerves	After division of the pelvic nerves
14	Hypogastrics	(1) 7½ to 10 (2) Less than 7½ (3) 5 to 6 (4) Less than 6 (5) ,, ,, 7½ (6) ,, ,, 7½	(7) 15 to 17½ (8) 12½ to 15
23	Hypogastrics	(1) Less than 7½ (2) 7½ to 10 (3) Less than 12½ (4) ,, ,, 12½ (5) ,, ,, 12½	(6) 16½ to 17½ (7) More than 15 (8) ,, ,, 15
25	Hypogastrics	(1) Less than 10 (2) 7½ to 10	(3) 20 to 22½
31	Hypogastrics	(1) 7½ to 10 (2) 7½ to 10 (3) 13 to 14	(4) 15 to 20 (5) 15 to 17½ (6) 25 to 30
35	None	(1) 10 to 20 (2) Less than 12 (3) 15 to 20 (4) 12½ to 15 (5) 12½ to 15	(6) Less than 15
38	None	(1) 20 to 25 (2) Less than 10 (3) 5 to 7½ (4) Less than 7½ (5) ,, ,, 7½	(6) 10 to 15 (7) 10 to 12½
66	Hypogastrics and pudics	(1) 10 to 15 (2) Less than 10 (3) ,, ,, 10	(4) 17½ to 20 (5) 17½ to 20

Therefore in six out of the seven experiments there is a well-marked increase in the intravesical pressure necessary to force open the urethra after division of the pelvic nerves. In the remaining experiment, the fifth, there is no such increase, this cat had an infective cystitis and it was the only one of the seven which had.

Three other experiments were made in a slightly different way. The spinal cord was transected in the last thoracic or first or second lumbar segments and the inferior mesenteric ganglia excised under chloroform and ether. After an interval of three weeks or more chloroform was given, the pudic nerves divided, the pelvic nerves exposed and a cannula tied into the fundus of the bladder at the attachment of the urachus. The cat was then decerebrated and the chloroform stopped. After an interval the bladder was emptied through the cannula and the latter connected with the same graduated warm water reservoir used in the previous series of experiments. By raising and lowering the reservoir the minimum pressure which gave rise to the escape of water from the external urinary meatus was found. The results are shown in the table.

Interval, in days, between the spinal transection and the decerebration	Nerves divided at the time of the transection	Minimum intravesical pressure, in centimetres of water, which lead to the escape of water from the urethra	
		Before division of the pelvic nerves	After division of the pelvic nerves
21	Hypogastrics	(1) 4 to 5 (2) 4 to 5	(3) 11 to 12 (4) 9 to 10
22	Hypogastrics	(1) 5 to 6 (2) 3 to 4 (3) 4 to 5 (4) 4 to 5	(5) 10 to 11 (6) 8 to 9 (7) 8 to 9
24	Hypogastrics	(1) 8 to 9 (2) 7 to 8	(3) 8 to 9 (4) 5 to 6

In the first and second experiments a well-marked increase in the intravesical pressure necessary to cause the escape of water from urethra followed division of the pelvic nerves. The third cat differed from the first two in having an infective cystitis; this had been present eight days. The cystitis was slight, œdema of the subepithelial tissue was present but no ulceration and the general health of the cat was unaffected; other reflexes from the bladder, such as the production of perineal contractions, were obtained in this cat.

In the ten experiments contained in these two series, therefore, there was an increase in the urethral resistance following division of the pelvic nerves except in the only two in which cystitis was present. It follows from this that there is a spinal reflex, having both paths in the pelvic nerves, evoked by distension of the bladder and effecting relaxation of the urethra.

A third set of experiments was done in the same way as the last two, except that instead of passing a catheter or of tying a cannula into the fundus of the bladder, the bladder neck was divided, a cannula tied into each cut end, and the cannulæ connected with vessels of warm water whose pressures could be altered at will by altering the water levels [Barrington 1921]. In these experiments no diminution of the urethral resistance could be found as the result of increasing the intravesical pressure. As the table shows, no increase in the minimal urethral resistance leading to the escape of water from the external meatus followed division of the pelvic nerves. It appears from the table that the urethral resistance left after the division of the pudic nerves increases in the course of thirteen to seventeen days, but this fact does not concern the present question.

The cannula tied into the distal end of the divided neck of the bladder in these experiments measured 7 mm. from its neck to its tip

Interval, in days, between the spinal transection and the decerebration	Nerves divided at the time of the transection	Minimum pressure in centimetres of water, which lead to the escape of water from the urethra.	
		Before division of the pelvic nerves	After division of the pelvic nerves
13	Hypogastrics and pudics	(1) 20 to 25 (2) 20 to 25	(3) 20 to 25
14	Hypogastrics and pudics	(1) 25 to 30 (2) 20 to 25 (3) 20 to 25	(4) 20 to 25
17	Hypogastrics and pudics	(1) 25 to 30 (2) 25 to 30 (3) 25 to 30 (4) 30 to 35	(5) 5 to 15
17	Hypogastrics and pudics	(1) 20 to 30 (2) 30 to 35 (3) 25 to 30 (4) 20 to 25	(5) 15 to 20
15	Hypogastrics	(1) 7½ to 10 (2) 5 to 7½ (3) 5 to 7½	(4) 5 to 7½
15	Hypogastrics	(1) 15 to 20 (2) 10 to 15 (3) 10 to 15 (4) 10 to 15	(5) 12½ to 15 (6) 12½ to 15
16	Hypogastrics	(1) 10 to 15 (2) 5 to 10	(3) 5 to 10

and 2½ mm. in diameter at its tip. Allowing for the part of the urethra between the ligature and the section and for the part held open by the end of the cannula, at least 1¼ cm., or approximately one-third, of the urethra is mechanically thrown out of action at its proximal end. In order to determine whether the increase in urethral resistance following division of the pelvic nerves was absent in these experiments because of the functional absence of the proximal third of the urethra, or because of the dissection of the bladder neck which was made in them, but not in the previous experiments, five further experiments were made. These were made in exactly the same way as those of the second series described, by using a single cannula tied into the fundus of the bladder, with the single addition that the neck of the bladder was exposed just before the decerebration and a hook put round it and withdrawn. The results of these five experiments were that an increase in the urethral resistance followed the division of the pelvic nerves in three experiments, a diminution in one and no alteration in the fourth. Cystitis was not present in any of the four. It therefore seems that the preliminary dissection of the neck of the bladder must interfere with the usual result of dividing the pelvic nerves in a considerable proportion of cases, but not in such a proportion as to completely abolish it in seven successive experiments. The part of the urethra chiefly concerned in the increased resistance is therefore the proximal third.

It is concluded that a sixth reflex exists, which is spinal. It is evoked by distending the bladder and effects a relaxation of the plain muscles of the urethra, chiefly or entirely in its proximal third. Both its paths are in the pelvic nerves.

In the second series of experiments, that in which the single cannula was tied into the bladder fundus, it was seen that individual intravesical pressures, lower than that which caused the escape of water from the urethra, were not associated with a significant increase in the corresponding bladder volumes after division of the pelvic nerves. This does not show that there is no spinal reflex contraction of the bladder evoked by distension, but it does show that if such exists it cannot be a factor in the increase of the residual urine resulting from division of the pelvic nerves, described at the beginning of this paper, until the abolition of the sixth reflex has given it a chance of showing itself.

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PART II.

If the spinal cord is divided in posterior thoracic or anterior lumbar region and the bladder emptied at the time of the operation, urine is not usually passed for three or four days. The cat then becomes soaked with urine, and contractions of the perineum occur at irregular intervals. Urine comes away very frequently in very small amounts, usually in association with perineal contractions. The residual urine increases for a day or two after the urine has first started to overflow. This first stage of retention with overflow is associated with hæmaturia in a considerable proportion of experiments. Perineal contractions may be evoked by squeezing the distended bladder before urine has begun to overflow. After the latter has occurred, squeezing the bladder leads to an increase in the frequency of the perineal contractions, and, with a longer time or more pressure, to the escape of urine from the urethra in a series of jets having the same periodicity as the perineal contractions. The resistance of the urethra can be felt to be very strong and to be stronger in males than in females, it can be felt to diminish during the time each jet is escaping. It is not possible, at this stage, to empty the bladder with any moderate pressure without a general anæsthetic, since when the bladder has become less tense from the loss of urine the urethral resistance can be felt to have increased. As far as can be felt, the urethral resistance can be made to vanish, without any preliminary diminution, if chloroform is given ; the bladder can then be emptied by squeezing it with quite low pressure. The abolition of the palpable urethral resistance with chloroform does not occur until about the time at which respiration stops, more often a few seconds after than a few seconds before, and when it occurs a few seconds before, respiration generally ceases even though the administration was stopped directly the urethral resistance vanished. The urethral resistance, having been abolished with chloroform, remains absent for at least a minute after spontaneous respiration has become re-established. The palpable urethral resistance of an intact cat behaves in the same way under the influence of chloroform.

At the end of the first week the condition is markedly altered, whether the overflow has been allowed to continue all the time, or whether the cat has been once chloroformed and the bladder completely emptied, in which case it will have begun to overflow for the second time. The residual urine and the palpable urethral resistance are now both diminished, and, in consequence of the latter, it is generally easy to empty the bladder without giving chloroform.

By the end of the second week there is a still further reduction in the volume of residual urine, and in a palpable urethral resistance. The urethral resistance is now commonly only just palpable, but its existence is quite obvious from the fact that when the bladder is squeezed the urine escapes in jets, as it did in the first stage. From this period onwards the urethral resistance remains the same, as far as can be felt, but the residual urine often increases in volume in the fourth or fifth weeks, but it never again reaches that which it was at the beginning of the overflow.

The cat has now arrived at the so-called automatic micturition stage, which is permanent unless modified by the supervention of some pathological condition. It is evident that the lowered urethral resistance is an important, and possible that it is the only, factor in the transition from the stage of retention with overflow to that of automatic micturition. It is the purpose of the present paper to inquire into what the lowered urethral resistance is due.

The urethral resistance, felt so readily in the stage of retention with overflow, and, less easily, in the stage of automatic micturition, must be due to the contraction of the compressor urethræ, since, after a spinal transection the urethra proximal to the compressor urethræ is full of urine at other times than when urine is being passed (Barrington, 1914). This being so, the resistance must be maintained through efferent fibres in the pudic nerve. If both pudic nerves are divided at the same time as, or previous to, the spinal transection, it is found that the overflow of urine occurs sooner, and, as soon as it has occurred, the urethral resistance which can be felt on squeezing the bladder is very low or absent. The observations of Masius (1868) on rabbits and dogs pointed to the same conclusion. He showed that the urethral resistance following spinal transections in front of certain levels was abolished if the cord behind such a transection was destroyed.

Many experiments were made by excising the inferior mesenteric ganglia at the same time as the spinal transection was made. The results did not differ qualitatively from those of the transection alone. It did appear that the diminution in the urethral resistance and in the volume of residual urine occurred rather more quickly, that the final volume of residual urine in most cases was rather less, and that hæmaturia in the retention and overflow stage was less frequent; in any case these quantitative differences were small, and it is possible that enough experiments were not done to establish their existence at all.

It has been shown previously (Barrington, 1914), that a firm, persistent contraction of the compressor urethræ occurs after division of the dorsal sacral roots on both sides and that this remains unaffected by subsequent division of the hypogastric nerves. The contraction of the compressor urethræ is maintained, therefore, after division of the afferent fibres in the pudic nerve but not after division of the efferent fibres.

The diminution of the contraction of the compressor urethræ following a spinal transection might be due to weakening of the muscle or to an increase in the effect of one or more of the reflexes which normally relax it. If the former supposition be true, division of both pelvic nerves would appear unlikely to prevent the diminution in urethral resistance following a spinal transection and could not possibly restore the urethral resistance after the diminution had taken place. On the other hand, if the fifth reflex, mentioned at the beginning of this paper, is acting more effectively, division of both pelvic nerves at the time of the transection should prevent the diminution in urethral resistance occurring, and division after the diminution has taken place should restore the resistance to its original strength.

Spinal transection subsequent to, or at the same time as, division of both pelvic nerves was found to be a very fatal operation by reason of the effect on the bladder. Only two cats so operated on survived more than a week, which is the least period from which any conclusion can be drawn. In one of these the urethral resistance remained very great up till the thirteenth day, had diminished but was still considerable on the fifteenth and was nearly absent on the sixteenth when cystitis was obvious and the cat was killed. In the second the resistance remained very great until the tenth day when the cat was accidentally killed with chloroform which was being given for the purpose of emptying the bladder. In both cats, therefore, the urethral resistance remained strong far longer than would have been the case if the pelvic nerves had been intact.

Hæmaturia is not uncommon after simple spinal transections but, at least in female cats, is seldom serious and only very rarely fatal. The bladder, when the condition is present, shows numerous small ecchymoses which are just beneath the epithelium. The epithelium over them is shed in places. The condition, therefore, arises from rupture of vessels forming the plexus immediately deep to the epithelium: these vessels are all small. When the transection is combined with division of the pelvic nerves hæmaturia is much more frequent and quite commonly fatal. In the fatal cases the animals show no local symptoms but become listless and drowsy and die in a few hours. The bladder in such cases is purple in colour and its walls are lax and infiltrated with blood throughout. The bladder contents may contain organisms in animals that have died. If the cat is killed as soon as it shows signs of illness, though the changes in the bladder wall are well-advanced, no organisms can be found in its contents, obtained aseptically, either in films or by culture on agar: the condition is, therefore, primarily mechanical and not primarily infective. Sections of the bladder at this stage show that the epithelium is largely shed and that small vessels immediately deep to it are greatly distended with blood, a large amount of extravasated blood is present between the muscular fasciculi and in the areolar tissue on their internal surface and that in places the muscle fibres are fragmented and stain badly, their nuclei having become cork-screw-shaped and in places granular. These appearances show that the condition is due to rupture of the large vessels which are situated in the areolar tissue close to the internal side of the muscle leading to necrosis of the bladder. The only mechanical condition present capable of producing this change is distension of the bladder. This, therefore, must be greater or more prolonged after the pelvic nerves have been divided with the transection than after the transection by itself.

In three cats, which had had a transection in the last thoracic or first lumbar segment, the pelvic nerves were divided after an interval of fourteen to forty-five days. In all there was a great increase in the urethral resistance easily palpable on squeezing the bladder, and this remained high until the animals were killed on the fourth to the twelfth days after division of the nerves. The increase of urethral resistance following division of the pelvic nerves was measured in three cats which had had transection in the first lumbar segment and excision of the inferior mesenteric ganglia twelve to sixteen days previously. The cats were decerebrated. In two a cannula was tied into the bladder fundus and connected with a warm water reservoir which could be raised and lowered and the lowest pressure which led to the escape of water before and after the division of the pelvic nerves noted. Division of the pelvic nerves was followed in one by a rise of urethral resistance from 5 to 6 cm. of water to 23 to 24 cm. of water, and in the other by a rise from 7 to 8 cm. to 30 to 31 cm. In the third cat the bladder neck was divided and cannulæ tied into each cut end. The water pressure necessary to force the urethra was measured before and after division of the pelvic nerves with the bladder pressure at 10 cm. of water. It was 15 to 17½ cm. before and 25 to 30 cm. after division of the nerves.

Division of the pelvic nerves, therefore, at the time of a spinal transection prevents the diminution in the urethral resistance, which would otherwise follow the transection, from occurring, and division of these nerves after the diminution of the resistance has taken place restores it. It is therefore concluded that the diminution in the urethral resistance following the transection results from an increased effectiveness of the fifth reflex mentioned at the beginning.

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KORSAKOFF'S SYNDROME: ITS HISTOPATHOLOGY.

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INTRODUCTION.

MUCH confusion still appears to exist regarding the clinical and pathological entity of the syndrome which Korsakoff described in 1887, and to which Jolly, at the Moscow Medical Congress of 1897, gave the name "Korsakoff's disease." This designation is untenable in the modern sense of the term "disease," for Korsakoff himself described the syndrome as occurring during the course of many different clinical conditions. As Korsakoff's original paper in Russian is unobtainable in this country it is difficult to be certain of his exact description of the syndrome, for in his later contributions to German journals [13], [14], he refers constantly to his original paper without precisely indicating its contents. But from his articles, and from those of Serbski [28], his co-worker, it is clear enough that what Korsakoff observed and described was a peculiar psychical state characterized by amnesia, disorientation in time and space and a tendency to fabrication, associated with the symptoms and signs of a peripheral neuritis. To-day the terms "Korsakoff's syndrome" or "Korsakoff's psychosis" are used indiscriminately, especially by psychologists, to denote any condition in which a psychical disturbance of this particular type occurs; the physical side of the syndrome may be ignored, or receive scant attention. If we are to use the term "Korsakoff's syndrome" at all, it should be restricted to the condition which Korsakoff observed and not applied only to the psychical state which occurs in that condition.

We began this study of a series of cases of Korsakoff's syndrome in order to determine whether any constant histopathological changes in the brain which might account for the peculiar psychical disturbances could be revealed by modern staining methods. We were at once faced by the difficulty of deciding which cases in the literature could properly be included under the syndrome. It became necessary, in order to limit our review of the pathological findings which have been described in psychical states resembling those found in the true Korsakoff syndrome, to ignore those cases in which there were no definite clinical signs of a peripheral neuritis or in which the diagnosis of peripheral neuritis was not confirmed by subsequent pathological investigation.

The conception that Korsakoff's syndrome is associated particularly with the peripheral neuritis caused by alcohol poisoning is fostered by the fact that this is perhaps the most common of all forms of neuritis. Although in the five cases of Korsakoff's syndrome we have to record the cause of the peripheral neuritis was alcoholism, an analysis of the literature revealed many causative factors other than alcohol, and we regret that we have not had the opportunity to include in our series cases in which another factor than alcohol was present.

ÆTIOLOGY.

It is pertinent to discuss shortly the ætiology of Korsakoff's syndrome before attempting to discuss the lesions which have been recorded pathologically, because the earliest pathological investigation which Korsakoff [13] carried out was on a case which developed after an extra-uterine pregnancy. Only later did he examine the nervous system of alcoholics who succumbed. From Korsakoff's own work and from the work of many subsequent observers, there can be little doubt that a toxæmia is the essential factor in the production of the syndrome, the nature of the toxin depending on the disease from which the patient suffers or on the poison which has been absorbed. Amongst many cases which Korsakoff reported clinically in which an endogenous toxin produced the typical syndrome, he mentioned puerperal fever, septicæmia, typhoid, typhus, diabetes, jaundice, lymphadenoma, tuberculosis, and certain cases of tumour, of which Serbski also gave an example in the case of a woman in whom the syndrome developed immediately after an operation for the removal of an ovarian dermoid.

Korsakoff [14] pointed out, however, that although the nervous system appeared to be particularly susceptible to the effects of alcohol, in that a large proportion of cases occurred in alcoholics, it might well be that the effect of the alcohol was to render the nervous tissue more liable to damage by other toxins, and that alcohol itself was not essentially the toxin responsible.

The recent work of Marcus [18], [19], [20], appears to confirm Korsakoff's view. Marcus reported twelve cases, in three of which the alcoholic factor could definitely be excluded, these being cases of beri-beri, influenza and encephalitis lethargica. But in all the alcoholic cases other disease processes were also operative, which included syphilis, pneumonia with nephritis, diabetes, acute pleurisy, acute nephritis, polyarthritis with jaundice, hepatic disease (probably cirrhosis). From this series of cases Marcus concluded that another factor besides alcohol was necessary for the production of the syndrome, and that this factor may sometimes give rise to the syndrome in the absence of alcoholism.

The evidence that the syndrome is primarily due to a toxæmia rests upon the fact that although it has been observed in severe forms of nearly every known disease (Mourreye [25], described a case which occurred during a severe attack of scarlet fever), it occurs most frequently in the common conditions in which a toxic factor is supposedly present, such as alcoholism and the toxæmias of pregnancy, especially hyperemesis gravidarum. Before Korsakoff described the syndrome it had been known for some years, as Ely [5] rightly maintained, that psychical disturbances accompanied by peripheral neuritis might occur in women who suffered from excessive vomiting during pregnancy, but the syndrome had not been described as a clinical entity until Korsakoff published his paper. Since then the subject of the occurrence of the syndrome in pregnant women has been fully dealt with by Von Hösslin [11], in his paper on the nervous complications of pregnancy, and a large number of cases has been recorded by various observers, notably by Ledoux [17], Ely [5], Weill-Hall et Layain [32], Dupouy et Courtois [4]. In all these cases the syndrome followed pernicious vomiting and nearly all the patients recovered after the pregnancy had been terminated either by delivery or by therapautic abortion. When death ensued, exhaustion rather than the neurological symptoms was accepted as the cause.

Much attention has been focused during the last decade on the subject of subarachnoid hæmorrhage, and Goldflam [7] was the first to draw attention to the fact that Korsakoff's syndrome is a common sequel to this vascular accident. The syndrome does not develop immediately after the hæmorrhage, but about three weeks later. Hall [10] described two cases of subarachnoid hæmorrhage in both of which the syndrome developed three weeks after the hæmorrhage. This late onset of the syndrome lends support to the essential presence of a toxic factor in the production of the syndrome, since presumably it is the absorption of disintegration products of the shed blood which gives rise to the syndrome. Goldflam maintains that as the prognosis in cases of subarachnoid hæmorrhage which develop a Korsakoff syndrome is good the changes in the brain must be of a recoverable nature.

Speculation on the nature of the toxic factor in other conditions in which Korsakoff's syndrome occurs would be valueless. But in the alcoholic cases it is probable that, as Marcus [18] suggests, another factor is always operative. Alcohol is not a cumulative poison and excretion is very rapid. Yet in most of the alcoholic cases there is a history of continuous steady drinking for many years until the syndrome develops and then in the fatal cases the course of the disease is short. If defective excretion of the alcohol were responsible for the rapid course of the symptoms, the condition might reasonably be expected to resemble that of acute alcoholic poisoning. There is no similarity however. Nor is there any resemblance to simple chronic alcoholism. It is reasonable to suggest that the imbibition of alcohol in sufficient quantities over a prolonged period lowers tissue resistance and permits degeneration of the nervous system to take place through the action of toxins, or through lack of essential nutritive factors.

PATHOLOGICAL LITERATURE.

The majority of pathological investigations which have been made have been on alcoholic cases and we propose to confine our review of the pathological findings to these cases, but we include the first pathological record of a case presenting the syndrome because Korsakoff [15] himself described it.

The case was that of a woman who developed the syndrome following an operation for an ectopic gestation. She died two months later, remaining in the same psychical state until death, whilst the neuritis was slowly progressive. Microscopically the brain showed no changes whatsoever. (The only stains were those of Weigert and carmine.) There was an increase of the connective tissue of the column of Goll in the spinal cord and a widening, either congenital or due to artefact, of the central canal. The third, fifth, sixth, eighth and tenth cranial nerves showed Wallerian degeneration with Marchi's method, that in the vagus being the most severe. There was a simple parenchymatous degeneration in the peripheral nerves, more advanced distally than proximally. The muscles had undergone a simple atrophy.

In an alcoholic case, of which only a short summary is given, Korsakoff and Serbski [15] found a thickening of the cortical vessels and an increase in the connective tissue (? neuroglia) of the cerebral cortex.

Ballet et Faure [1] reported two cases with post-mortems. In both there was fatty degeneration of the liver and in one a slight cirrhosis.

The pyramidal cells in the motor cortex were chromatolytic. No other changes were found in the brain. In one case the anterior horn cells in the lumbar region of the spinal cord were also chromatolytic; in the other they appeared normal. No degeneration of the posterior columns of the spinal cord was found in either case. In both cases there was degeneration of the peripheral nerves.

A. Meyer [23] in discussing "axonal reaction" described the Betz cells which he observed in the motor cortex of a patient who had exhibited Korsakoff's syndrome during life as examples of this reaction. He found similar chromatolysis in the cells of the frontal region, and in all the nuclei of the medulla, except the hypoglossal. A few degenerating fibres were seen in the crus, in the splenium of the corpus callosum and in the thalamus, but these did not correspond to the great degeneration of the pyramidal cells in the cortex. Meyer did not regard this finding of degenerate pyramidal cells as peculiar to the pathology of the Korsakoff syndrome, as he had found the same degeneration present in most forms of insanity. Turner [30] also found degeneration of the Betz cells in a case in which he examined the brain, but he considered that this was consecutive to the extensive degeneration of the crossed pyramidal tracts which was present in the spinal cord. Turner also found degeneration of the posterior columns of the spinal cord and made the statement, which we have been unable to confirm, that every case presenting the Korsakoff syndrome examined pathologically up to that time had shown degenerative changes in these tracts. The anterior horn cells in the lumbar region were extensively degenerated and a large proportion of the cells of the dorsal root ganglia appeared chromatolytic. Turner [31] regarded the appearance of these cells as due to "axonal reaction." Marchi degeneration was present in the peripheral nerves.

Cole [3] gave a very full and detailed account of the changes he found in the nervous system of two patients. He also found acute cell degeneration in the Betz cells, in the cranial nerve nuclei and in the anterior horn cells of the spinal cord. In one case there was a slight atrophy of the tangential fibres in the cortex. In both cases there was extensive degeneration of the posterior columns of the spinal cord throughout its length. Degeneration of the pyramidal tract was also seen at all levels. The peripheral nerves and the vagus nerve all showed degeneration by Marchi's method. The muscles had undergone fatty degeneration. Cole considered the affection to be polyneuronal rather than polyneuritic.

Mott [24] examined the nervous system in two fatal cases of Korsakoff's syndrome. He found that the brains did not show obvious signs of cerebral wasting. The microscopic changes consisted in slight wasting of the tangential, supraradial and interradial fibres of the cerebral cortex; otherwise the fibre tracts were normal except in very severe cases in which there was degeneration in the posterior roots and columns of the spinal cord. There was acute chromatolysis of the Betz cells and of the anterior horn cells of the spinal cord. The cytoplasm of these cells contained an excess of pigment. Mott also found changes in the vessels in the cortex. Their walls were undergoing fatty degeneration, and around some vessels were hæmorrhages. Mott maintained that the changes he found in the brain were due to functional deterioration of the cortical neurones caused by a poison circulating in the blood, and that these changes were not necessarily permanent, but recoverable. Gudden [9] examined four cases pathologically. He found atrophy of the tangential fibres in the third frontal convolution; disappearance of the Nissl bodies from the large nerve cells in the cortex; thickening of the cortical blood-vessels with hyaline degeneration of their walls. Gudden considered the loss of tangential fibres the earliest and most constant lesion.

Marcus [20] studied the pathological changes in five cases. The acute cases showed different changes from the chronic cases. In the acute cases the lesions were confined mainly to the frontal region and to the deeper layers of the cortex. No degeneration of fibres was observed. Many small vessels in the cortex were thrombosed and the tissues around them stained badly; the nerve cells being degenerate and undergoing phagocytosis. The zona multiformis contained many degenerate cells. Degenerate cells were also seen in the corpus striatum. The spinal cord and nerves were not examined in the acute cases. In the chronic cases the brains were much atrophied. Most of the external layers of the frontal cortex were transformed into a reticulated tissue, the normal architecture of the cortex being hardly recognizable. Many newly-formed vessels were present, of which some were thrombosed. A few miliary necroses were present. The ganglion cells were disintegrated but little neuronophagia was to be seen. In the basal nuclei miliary necroses were observed. Marcus concluded that the outstanding lesion in Korsakoff's syndrome was a parenchymatous degeneration in the cerebral cortex. The changes were greatest in the deepest layer of the cortex, and only slight in the superficial layers, whilst the predilection of the process was for the anterior part of the frontal lobes.

The largest series of cases examined pathologically is that of Gamper [6], who examined the brains of sixteen patients who had died from chronic alcoholism with "Korsakoff's psychosis." In most cases the psychosis was of acute onset ending in death after eight to fourteen days. In three cases the patient lived for two months and in one case for nine months. Gamper found that the cerebral cortex was normal in all his cases. The most striking changes were seen in the mid-brain. Gamper described two types of lesion: (1) great proliferation of the endothelial and muscular walls of the blood-vessels with neuroglial overgrowth and secondary destruction of the nerve cells in the nuclei, especially of the inferior corpora quadrigemina and the corpora mamillaria; (2) irregular areas of porosis in which were thickened blood-vessels with proliferation of their endothelium. The latter type of lesion was found mainly in the central grey matter of the mid-brain. No inflammatory reaction was observed, and the nerve cells appeared healthy where they were not pressed upon by neuroglial overgrowth. Gamper considered that the disease process was a local elective one, not exclusively, but most severely incident upon, the vegetative nervous system. The spinal cords and nerves were not examined in this series.

CASE REPORTS WITH PATHOLOGICAL EXAMINATION.

Case 1.—S. H., a single man, aged 40, was admitted to the National Hospital under the care of Dr. Riddoch on October 25, 1930. The history obtained from the patient was unreliable owing to obvious gross lapses of memory, especially in relation to intervals of time. The patient was incapable of making spontaneously any but the simplest possible statements. Direct questioning elicited the following story: For three to four weeks past he had had practically no food, but had been drinking large quantities of whisky. He spoke as if he realized that his present trouble was due to this. At the end of the orgy intermittent pains were felt all over the body, particularly in the legs. The character of the pains was not described, but was definitely said not to be "shooting" in character. The patient also complained of loss of appetite, of general "shakiness" and of passing "smoky" urine. Time intervals were given, but they were hopelessly contradictory. The onset of symptoms was probably from three to five weeks before admission. Two weeks before admission, he began to "go off his legs." The arms too became progressively weaker, but he said that he was actually confined to bed only one day before he came into hospital.

Past illnesses: none except a left mastoidectomy fourteen years before. On examination, the patient was seen to be a flabby-looking, obese, middle-aged man. His face was pale and puffy, but there was no local or generalized œdema. Speech was slurred. The mental state was apathetic. The patient did not appear cognizant of the gravity of his condition. He was co-operative and correctly orientated when first examined and had no delusions or hallucinations There was no obvious confabulation or confusion at this time; but memory was poor for the details of his history and his statements were unreliable owing to self-contradiction.

The optic discs were normal. The pupils were slightly irregular in outline and reacted sluggishly to light, both direct and consensual. The corneal reflexes were both absent. There was deafness on the left side. Both trapezii were very weak: hardly any contraction could be obtained on either side. Generalized tremor of the tongue was present.

The arms and legs were almost completely powerless and lay flaccidly on the bed. Any movement that was possible was interrupted and short-lived. Some power of grasp and of extension of the fingers was retained. The feet could only just be moved, but plantar flexion was much better than dorsiflexion. All the limbs were toneless. There was no obvious atrophy, fibrillation or tremor. The patient could raise his head off the bed, but the abdominal muscles did not contract when this movement was carried out.

Sensation was difficult to test as the patient was an unreliable witness. There was, however, a diminished response to stimulation by pin-prick and cotton-wool on the legs as compared with the arms. Hypalgesia of the legs was greater peripherally than proximally. Vibration sense was also diminished in the legs as compared with the arms. Deep pressure sensibility was hyperacute in both arms and legs, especially in the calf muscles. The deep and superficial reflexes were all absent.

No abnormalities were detected in the cardiovascular and respiratory systems. There was some tenderness to moderate palpation in the right hypochondrium, but no rigidity. The liver margins were normal to percussion.

On the day after admission the patient became confused and disorientated. One minute he said that he had walked up to hospital that day, the next that he had been in hospital three or four days. He also became excitable and restless. He admitted that he had drunk $\frac{3}{4}$ bottle of whiskey a day but said that he had stopped drinking "a long time ago." (A message from his private doctor stated that he had been drinking a bottle of whiskey a day as recently as the day before admission.) Next day the patient became more confused, rambling in his statements and violent. His temperature rose to 102° F. He died very suddenly on October 28, three days after admission.

A post-mortem examination was performed thirty-six hours after death by Dr. J. G. Greenfield.

Post-mortem notes.—The body was that of a well-nourished man with no evidence of œdema. On removal of the brain and spinal cord the brain appeared pale and œdematous. Several peripheral nerves were removed for section. The lungs were œdematous and congested. The heart appeared healthy but flabby. The liver was pale with a central pallor in each lobule which apparently represented a fatty change. The kidneys and spleen appeared normal. Nothing remained of the suprarenals but empty capsules.

PLATE IV.

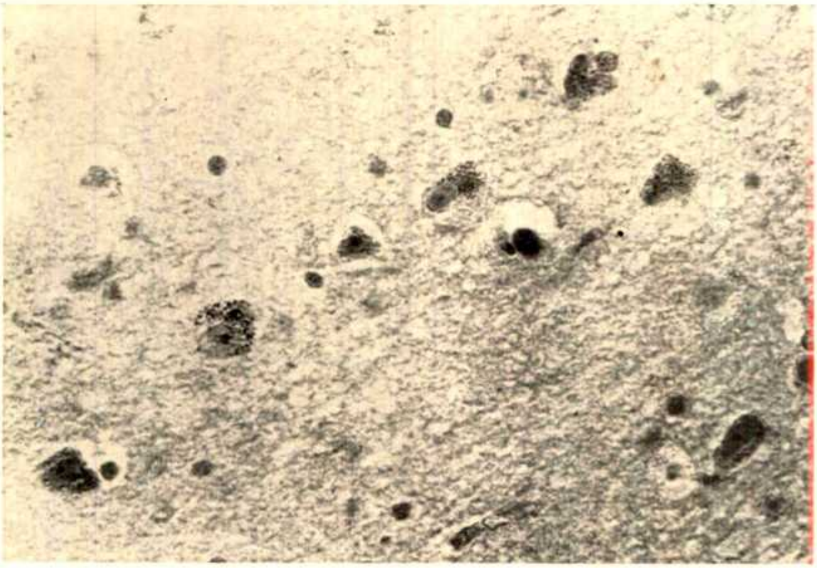
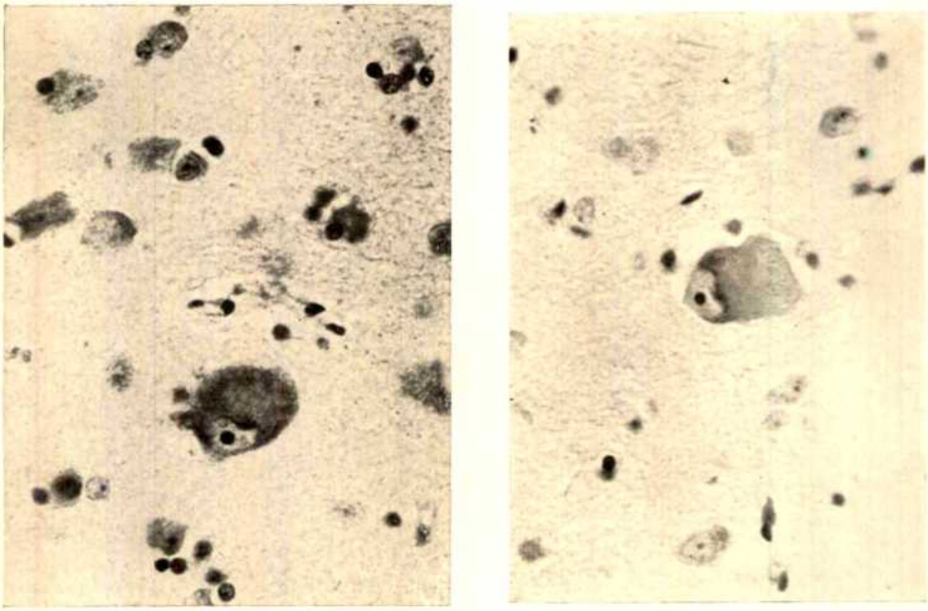


FIG. 1.—Section from prefrontal cortex of *Case* 1 stained with Scharlach R. and hæmatoxylin, to show the large accumulation of lipochrome in the nerve-cells.



FIGS. 2 and 3.—Sections from the motor cortex of *Case* 4. Two Betz cells are seen undergoing chromatolysis. In fig. 2 accumulations of lipochrome granules are visible in the Betz cell and in one or two of the smaller nerve cells. (Celloidin section, stained with toluidin blue.)

To illustrate paper by Carmichael and Stern.

Microscopical examination.—Sections of the liver showed advanced fatty degeneration of the liver cells with early periportal fibrosis.

The heart muscle appeared normal.

The nervous system in all our cases was examined by a variety of staining methods. The following methods were employed on every case. Scharlach R., Bielschowsky, toluidin-blue (Nissl), Cone and Penfield's modification of Hortega's method on frozen sections; Weigert-Pal or Loyez' stain for myelin, toluidin-blue, Marchi, hæmatoxylin with van Gieson's counterstain on celloidin sections. In three cases Marinesco's method for the demonstration of senile plaques was used. The cerebral cortex when stained with Scharlach R. presented a striking appearance. Heavy deposits of a lipoid which stained bright orange with Scharlach R. surrounded nearly all the blood-vessels in the grey matter and most of those in the white matter. Both the large and the small nerve cells in the prefrontal and motor areas contained numerous droplets of a lipoid which gave a similar coloration with Scharlach R. to that around the blood-vessels. Deposits of this lipoid were also present in the neuroglial cells of the superficial layers of the cortex in these two areas. The lipoid appeared in many situations almost completely to fill the cell body. This is shown in fig. 1. The amount of lipoid was greatest in the cells of the prefrontal area, there was much less in the cells of the motor area. The size of the droplets in the nerve cells was rather larger than in the deposit which ringed the blood-vessels. Certain solubility tests and staining reactions which Hurst [12] used in his study of the lipoids in neuronic degeneration were carried out in an attempt to ascertain the nature of this lipoid. Before we consider these tests it is necessary to state that the deposits of lipoid in the nerve-cells and around the vessels occurred only in the cerebral cortex and in the olivary nuclei in the medulla (where a large amount of lipochrome is normally present). We could not find such deposits in the cells of the mid-brain, hypothalamic nuclei, pons or medulla. For comparison with the sections from this case we subjected to the same solubility tests at the same time sections from the cerebral cortex of a senile patient in which much lipochrome pigment was present in the Betz cells.

We found that immersion in absolute alcohol or acetone for twenty-four hours had no appreciable effect on the staining properties of the unknown lipoid; thereafter it still stained bright orange. Similarly, immersion in absolute alcohol for twenty-four hours after a preliminary treatment for twenty-four hours with saturated zinc sulphate failed to affect the staining reaction of this lipoid with Scharlach R. These tests indicated that the lipoid which we observed did not contain either true fats or fatty acids. Immersion in acidified absolute alcohol and ether for twenty-four hours had some effect on subsequent staining with Scharlach R. The coloration of the lipoid was paler and more yellow than in untreated sections; but not more so than in the sections which we used as controls and which we knew contained lipochrome. As the unknown lipoid was not doubly refractile and stained with Kultschitsky's hæmatoxylin, after five days' mordanting, we concluded that it possessed all the properties of lipochrome, as detailed by Hurst, and was in fact that substance. Although lipochrome itself is insoluble in a mixture of acidified alcohol and ether, the fact that it stains more faintly with Scharlach R. after treatment with these fat solvents calls for some explanation. That given by Greenfield and Holmes [8] in the section on lipoid deposits in their paper on Amaurotic Familial Idiocy seems in accordance with what is known about the mode of action of Scharlach R. This dye does not act as a stain but becomes dissolved in any fatty substance present. According to Greenfield and Holmes, although the lipochrome is not dissolved by alcoholic solvents the dye is unable to act owing to the removal of normal myelin by these solvents. The rapid wash in 70 per cent. alcohol which the sections are given after immersion in Scharlach R. is sufficient to dissolve out the dye from the nerve cells when no other parts of the sections are holding it. The resistance of lipochrome to fatty solvents may be gauged from its presence in celloidin sections stained by the Nissl method, as greenish-grey granules. We observed these granules in the nerve cells of the cortex, particularly of the frontal region, in this case; they corresponded to the droplets of lipoid seen in frozen sections with Scharlach R.

The appearance of the nerve cells in the cortex was relatively normal. Certain large nerve cells in the prefrontal cortex and one or two Betz cells in the motor area had eccentric nuclei which lay against the cellular membrane and were oval or crescentic in shape, but these abnormal cells were few in number compared with those in our other cases. There was no perivascular infiltration or satellitosis and the blood-vessels of the cortex appeared healthy. The cortical fibres were well myelinated.

We paid particular attention to sections of the thalamic nuclei and corpora mamillaria in this case, as Gamper has reported a degeneration of their cells in Korsakoff's syndrome which he considers an essential lesion. Although we found that all the nerve cells in the thalamic nuclei and corpora mamillaria were rounded or had only one or two short processes, whilst their nuclei were slightly eccentric and the Nissl granules were in "clumps" rather than in a regular pattern, yet two normal corpora mamillaria from cases in which the sole lesions were in the spinal cord presented exactly the same appearance. We therefore concluded that the appearance of these cells in the alcoholic case could not be accepted as evidence of degeneration of the cells. We have been confirmed in this opinion by illustrations of the normal histology of the corpora mamillaria and thalamic nuclei in the recent "Handbuch der Mikroscopischen Anatomie des Menschen." The basal ganglia, mid-brain, pons and medulla did not show any abnormalities.

The only departure from the normal which we observed in the spinal cord was in Nissl sections at the level of the fifth lumbar segment and from the cervical enlargement. In these sections the anterior horn cells showed early chromatolytic changes.

The only peripheral nerve available for section was a small portion of the popliteal. No interstitial changes were seen in sections of this nerve stained by hæmatoxylin and van Gieson, but Kernohan's modification for celloidin sections of Bielschowsky's method showed degeneration of many axis cylinders. A portion of muscle from the calf was sectioned. The muscle-fibres appeared normal in size and shape. There was no increase in the number of sarcolemmal nuclei and no fibrosis.

Case 2.—R. C., married man, aged 48, was admitted to the National Hospital under the care of Dr. Riddoch, on October 25, 1928. He complained of weakness and pains in the limbs and loss of appetite. In addition, the history was obtained from a relative that defective mental concentration had been present for the past ten years, gradually increasing in severity, and culminating during the ten days prior to admission to hospital in systematized delusions and fabrication of elaborate stories. Two months ago the legs suddenly "gave way" and the patient had been unable to walk since. The pain in the legs was very severe and much worse on movement. He had taken very little food for some weeks. Incontinence of urine and fæces had been present for some days.

Sixteen years ago the patient had had malaria whilst out East and was sent home with "alcoholic paralysis" of the legs. He had walked with two sticks ever since. For the past ten years, up to June, 1928, he had drunk 1 to 1½ bottles of whisky a day and since then even more. He had had no other illnesses.

On examination the patient was found to be an obese unhealthy looking individual. He was not drowsy but very inattentive and slow-witted. He had varied and complicated delusions about his surroundings and associates, and was constantly under the impression that he was elsewhere than in hospital. Memory was poor for recent events, but much better for distant ones. The patient fabricated elaborate stories in order to get his own way. Speech was blurred and slovenly. There was a gross facial tremor.

Cranial nerves.—The optic discs were normal. The pupils reacted well to light, both direct and consensual, and to accommodation. Ocular movements were normal and the fields were full. Both corneal reflexes were present and equal. There was a generalized facial tremor, and generalized tremor of the tongue was also present.

The musculature of the limbs was poorly developed. Power in the arms was very weak, especially in the fingers and wrist. The patient could raise his head from the bed, but not his shoulders. Power in the legs was almost completely lost. There was complete double foot-drop with an early contracture of the calf muscles.

At the time of examination the patient did not complain of spontaneous pain or paræsthesiæ; but deep pressure on any group of muscles in the limbs gave rise to severe pain. There was peripheral diminution of sensibility to pin-prick and cotton-wool in all limbs and vibration sense was abolished in the legs. The arm, knee, ankle and abdominal reflexes were absent on both sides. The plantar responses were flexor.

The heart was not enlarged. The apex-beat could be neither felt nor seen.

The heart sounds were distinct and the rhythm "tic-tac." The blood-pressure was 110 systolic, 80 diastolic. The respiratory and alimentary systems appeared normal. Progress notes on October 29 stated that the patient was much troubled by insomnia and required nightly doses of 2 drm. of paraldehyde to induce sleep, which even then was fitful. Much of the night was passed in a mild mumbling delirium. Disorientation was not quite complete, although from time to time the patient insisted that he was either at home or abroad.

A progress note on November 5 reported that the patient had become very helpless. He was then sleeping badly even after paraldehyde. His mental condition was more abnormal in that his fabrications had reached a stage of astonishing complexity, and were completely free from any element of self-criticism. From this time the patient went downhill rapidly and died on November 14.

A post-mortem was performed thirty-six hours after death by Dr. J. G. Greenfield.

Post-mortem notes.—The body was that of a big fat man. The muscles of the arms below the elbow and of the legs below the knee were considerably wasted. Double foot-drop was present. On removal of the brain and spinal cord the veins over the vertex were seen to be considerably distended and the sulci were widened. There was some congestion of the veins around the theca in the lumbar region. No disease was evident in the cerebral vessels. The left lung was congested at the base. The heart was flabby and dilated, but the valves appeared normal. The aorta appeared remarkably healthy. The liver was small and pale. The kidneys and spleen were congested. The supra-renals appeared healthy. Portions of numerous nerves and muscles were taken for section.

Microscopical examination.—In sections of the liver an intense fatty degeneration of the epithelial cells was seen. Very few healthy cells remained. There was no periportal fibrosis. Fatty degeneration was also present in the heart muscle. In the kidneys there were degenerative changes in the convoluted tubules, many of which were completely disintegrated. The lungs were much congested. Many "heart failure" cells were present.

In the *nervous system* the most striking changes were seen in sections of the cerebral cortex stained by Scharlach R. method. Nearly every nerve cell, both large and small, contained numerous droplets of a lipoid substance which stained deep orange with the dye. In the more superficial layers of the cortex lipoid was present in and around neuroglial cells, but in the microglia rather than in the protoplasmic neuroglia. Considerable quantities of this lipoid, together with a large number of compound granular corpuscles, were found around the majority of blood-vessels in the cortex. No lipoid was seen surrounding the blood-vessels in the white matter. The region of the cortex in which most lipoid was present in the nerve cells was the prefrontal region. The Betz cells contained a large quantity of lipoid, but the smaller nerve cells in the motor region were comparatively free from the deposit. In the temporal and occipital regions, only the large nerve cells contained much lipoid, although there was some accumulation of lipoid around the vessels.

We employed the same solubility tests on sections of the cortex as we did in Case 1 in order to ascertain the nature of the lipoid; and we obtained the same results. After prolonged immersion in an acidified solution of absolute alcohol and ether it was still possible to obtain a bright yellow coloration of the lipoid with Scharlach R., not as brilliant certainly as in untreated sections, but quite as bright as the lipochrome pigment in control sections. We therefore considered that the lipoid present in the cortical cells of this case was also lipochrome, i.e., not an abnormal product of cellular metabolism, but a normal product present in abnormal quantities.

This production of abnormal amounts of lipochrome appeared to be confined to the cells of the cerebral cortex. The cells of the basal ganglia, mid-brain, pons and medulla did not contain more than a few granules of lipochrome, not comparable with the amounts present in the cells of the cortex.

In sections stained by the Bielschowsky method the neurofibrils of the cortical nerve cells seemed to be pushed to the periphery of the cells by the lipochrome deposits, but the intracellular course of the fibrils was easily discernible and they appeared normal. Neither by this method nor by that of Marinesco could we demonstrate senile plaques in the cortex.

The nerve cells in the prefrontal and motor areas of cortex, when stained by the Nissl method, displayed changes common to all our cases, but varying in the degree of severity. These changes involved not only the large nerve cells in these areas but, in this case, the smaller nerve cells in both areas, though particularly in the frontal region. Although the size of the Betz cells made the alteration in structure more obvious in them the cells in the prefrontal region were certainly as much, if not more, affected than those in the motor region. The affected cells appeared to be undergoing acute chromatolysis. Their processes were lost or shortened, their nuclei were crescentic in shape and lay eccentrically, often just under the capsule, whilst the Nissl granules were either confined to the periphery of the cells or had disappeared. But nowhere did we observe any evidence of satellitosis or phagocytosis of these apparently degenerate cells. Neither could we discover any "ghost cells" resulting from partial disintegration of the cells.

The hæmatoxylin and van Gieson stain revealed an intense engorgement of the cortical vessels, especially in the grey matter. The cortical arteries were slightly thickened. No perivascular infiltration was present in either the grey or the white matter.

The microglia appeared normal by Hortega's method. When stained by the Kultschitsky-Pal method the superficial tangential fibres of the frontal cortex appeared to be less numerous than normal. In part of their course these fibres displayed bulbous swellings, indicating an early stage in degeneration.

We could find no pathological changes by any method in the basal ganglia, the mid-brain, pons or medulla.

The spinal cord in the region of the cervical and lumbo-sacral enlargements exhibited severe axonal reaction. Numerous cells in the anterior horns were rounded and vacuolated, and contained either eccentric nuclei or were devoid of nuclei. There was no evidence of tract degeneration in the spinal cord at any level. The anterior nerve roots at all levels of the cord stained more faintly with Loyez' myelin stain than did the posterior roots.

The following peripheral nerves were examined: sciatic, median, ulnar, radial and internal cutaneous. The majority of the fibres in all these nerves were seen to be degenerating when stained by the Marchi-Busch method. The Weigert-Pal method demonstrated that many fibres had already reached an advanced stage of degeneration. In the sciatic nerve there was a slight perineural infiltration with small round cells. In the radial nerve early interfibrillar fibrosis was seen but no cellular infiltration. The other nerves did not show any reaction of the interstitial tissues. The degenerative process appeared to be a simple parenchymatous degeneration of the nerve fibres.

The biceps brachialis, tibialis anticus, soleus and biceps femoris muscles were examined. Many fibres of the soleus muscle had atrophied. There was no fibrous or fatty replacement of muscular tissue. No increase in sarcolemmal nuclei was noted. The gastrocnemius, tibialis anticus and biceps femoris all contained some atrophied fibres, but not so many as the soleus. The size of the fibres in the biceps brachialis appeared normal.

For the clinical and post-mortem notes on the two following cases we are indebted to Dr. W. Gordon Sears, Assistant Medical Officer at the Mile End Hospital.

Case 3.—A. L., a married woman, aged 43, was admitted to the Mile End Hospital on November 21, 1929. She complained of loss of power in the legs, especially on attempting to walk upstairs, the duration of this symptom being five weeks. She had had pains in the legs "on and off for years" and four years previously had been treated for this symptom and for "stomach-ache" in St. Andrew's Hospital. The pains in the legs became worse when the power in them grew weak. For two weeks prior to admission to Mile End Hospital the patient had been confined to bed and had been vomiting "on and off." Shortly before admission to hospital there had been loss of sphincter control. A relative gave the history that the patient had shown mental symptoms after the suicide of her father a short time previously. She had been a heavy whisky drinker at times, but was stated not to have been ever obviously drunk. The family history was essentially negative; she had had no children and no miscarriage. There had been no serious illnesses except a laparotomy and left ovariectomy.

On examination the mental state of the patient was found to be dull. She displayed little interest in her surroundings and apparently had some loss of memory, and some indefinite delusions about her husband.

The pupils were slightly eccentric and reacted sluggishly to light. The optic discs were normal. Nystagmus was present on looking to right and left and there was a slight weakness of the right external rectus muscle. The patient had been deaf for some time. There was bilateral wrist-drop with great weakness of the grip on both sides.

The power of movement of both legs was very poor. The calf-muscles were tender on deep pressure and there was diminution of sensation to pin-prick on the legs. Both knee- and ankle-jerks were absent. The plantar responses were doubtful.

No abnormalities were detected in the alimentary or respiratory systems. The heart was not enlarged but a systolic bruit could be heard over all areas. There was some pallor of the mucous membranes. A blood-count gave the following result: red blood-corpuscles, 4,270,000; hæmoglobin, 56 per cent.; colour index, 0·7; white blood-corpuscles, 17,480. Differential count: polymorphonuclears, 70 per cent. (12,236): lymphocytes, 16·5 per cent. (2,884), large hyalines, 13·5 per cent. (2,360). The patient died rather suddenly on November 24, 1929, three days after admission.

Post-mortem findings.—The brain and spinal cord showed no macroscopic abnormality. A small portion of the musculo-spiral nerve was removed for section. The thoracic organs all appeared healthy. The stomach presented the appearance of a chronic gastritis. The liver was pale and was evidently undergoing fatty degeneration. The gall-bladder and spleen appeared normal. The kidneys and bladder were congested, but otherwise normal.

Microscopical examination.—On section of the liver an intense fatty degeneration of liver cells was noted. A similar degeneration of the cells of the heart muscle was found, together with an early interstitial fibrosis.

In the *nervous system*, sections of the frontal and motor regions of the cerebral cortex when stained by Scharlach R. showed large accumulations of lipochrome pigment in the Betz cells and in most of the large nerve cells.

When stained with toluidin blue, several Betz cells were seen to possess eccentric nuclei and peripherally distributed Nissl granules, but the majority of the nerve cells in the cortex in this case appeared healthy. A few, however, in the motor region were surrounded by satellite cells, which appeared to be engulfing them. These satellite cells were shown by Cone and Penfield's modification of Hortega's method to be microglia. Most of the microglial cells were normal in shape, but one or two elongated forms with terminal processes only were seen. These abnormal forms occurred only in the motor area; we did not find them in the frontal region. No perivascular infiltration was observed, but the vessels in both the white and the grey matter were thickened. The cortical fibres were well myelinated. The neurofibrils of the cortical nerve cells appeared normal and we could not demonstrate senile plaques by either the Bielschowsky or the Marinesco method. No abnormalities could be detected in the basal ganglia, mid-brain, pons or medulla.

The sole pathological change we found in the spinal cord was early chromatolysis of a few anterior horn cells in the lower lumbar segments. The only peripheral nerve available for examination in this case was a small portion of the musculospiral. There was no evidence of degeneration in the part examined by the Marchi method, and no cellular infiltration or fibrosis was seen in that stained with hæmatoxylin and van Gieson. No muscle was examined in this case.

Case 4.—A. A., a married woman, aged 41, was admitted to the Mile End Hospital on August 29, 1930. She complained of the loss of use of her legs, pain in the shoulder and legs, and some numbness of the hands, feet and legs. The duration of all these symptoms was given as two weeks. The patient had been a regular spirit drinker "for some time." The family history was essentially negative; she had had eight children.

On examination the patient was found to be dirty in her habits. She was disorientated in time and space (gave day of week and name of hospital wrongly). She thought that the examiner had been to see her at her home and that he had met her son (pseudo-reminiscence). She was irrational and very noisy.

The pupils reacted sluggishly to light. The optic discs and the other cranial nerves appeared normal. Power in the arms was good, and there was some dubious diminution of sensation to pin-prick (patient was a poor witness). The arm-jerks were brisk. Power in the legs was poor. There was apparent loss of sensation to pin-prick over the whole of the lower limbs and over the trunk as high as the level of the nipples. The knee- and ankle-jerks were lost on both sides. The plantar responses were flexor.

The heart was not enlarged, but the first sound at the apex was accentuated. The heart sounds were obscured by coarse rhonchi all over the chest. The liver was just palpable below the costal margin. Blood Wassermann reaction was negative. The patient became more irrational and more noisy day by day and went downhill rapidly. She died on September 12, 1930.

Post-mortem findings.—Well-marked post-mortem staining was present and there was a slight redness of the skin over the sacrum.

On removal of the brain and spinal cord the arachnoid membrane covering the brain was more adherent than normal. There was some flattening of the convolutions and the brain appeared œdematous. The spinal cord presented no macroscopic abnormality. The cerebral vessels appeared healthy.

The lungs were congested but otherwise healthy. A few enlarged glands were present at the roots of the lungs. The heart was of average size and appeared normal except for a slight thickening of the mitral valve. The stomach was in a condition of chronic gastritis. The mucous membrane was atrophic and a number of small hæmorrhages were present in the wall. The liver was not enlarged but was very pale, due to fatty changes. The spleen was soft and diffluent. The kidneys and pancreas were healthy.

Microscopical examination.—Sections of the cerebral cortex stained with Scharlach R. presented the same appearance as did the cortex in the three cases previously described. The large nerve cells, particularly in the frontal cortex, were filled with a lipoid material which gave the solubility reactions of lipochrome. The smaller nerve cells in the frontal area and the Betz cells in the motor area, did not contain so much lipochrome as the cells in the frontal region, and the deposition of lipochrome in the glial cells of the superficial layers of the cortex was not so obvious as in our other cases.

The intracellular neurofibrils appeared normal by the Bielschowsky method, though in the frontal region they were displaced to the periphery of the cells by the lipochrome. We could nowhere in the cortex find any senile plaques.

When stained by the Nissl method, most of the large nerve cells in the prefrontal and motor areas were found to be in a condition of acute chromatolysis. Many of the small nerve cells in these areas presented the same appearance. The affected cells were rounded, their processes being shortened or lost; their nuclei were of bizarre shape and situated at the extreme periphery of the cell, just under the capsule, whilst the Nissl bodies were either completely lost, or more commonly arranged in finely granular masses at the periphery of the cell. Examples of these cells are well seen in figs. 2 and 3.

The alterations in structure of the nerve cells of the cortex in this case were more severe than in any of our other cases. But we could nowhere determine any evidence of neuronophagia or satellitosis; neither did the hæmatoxylin and van Gieson stain reveal any perivascular infiltration or changes in the blood-vessels. The lesions in the brain appeared to be confined entirely to the nerve cells of the cerebral cortex, since the Weigert-Pal method did not demonstrate any loss of myelinated fibres in the cortex and the mid-brain, the pons and medulla showed no abnormality by any staining method. The spinal cord was stained with Scharlach R. and with Loyez' stain for myelin, but neither of these stains revealed degeneration of fibre tracts at any level of the cord.

In the fifth lumbar segment, several anterior horn cells were seen by the Nissl method to be chromatolytic. At other levels of the cord these cells appeared normal.

The median, ulnar, sciatic and posterior tibial nerves were examined. Early degeneration was found in all these nerves by the Marchi method, but more advanced degeneration was present in the posterior tibial than in the other nerves. In the ulnar and median nerves the perineural spaces contained a small number of lymphocytes and large mononuclear cells. In the posterior tibial nerve, no infiltration with cells was observed, but there was slight proliferation of the cells of the sheath of Schwann.

The gastrocnemius and flexor digitorum communis muscles were examined. The fibres of the latter muscle were normal in size and shape. Those of the gastrocnemius were small and atrophic, the average size being 20 to 25 μ. There was an increase in the number of sarcolemmal nuclei, but no fibrosis or other interstitial change.

Case 5.—R.S., a married woman, aged 43, was admitted to St. Bartholomew's Hospital, under the care of Professor Fraser. The patient was incapable of giving a satisfactory history as she was in a somewhat stuporous condition, not realizing where she was, nor the time. Even to direct questioning no satisfactory or consistent replies were forthcoming. The relatives supplied the following history:—

Eighteen months previously the patient had been operated on for a pelvic condition. Following this she never quite recovered and "owing to her heart being weak" took brandy. This stimulant was changed to "bitters and ale" six months before admission. A few weeks after the alteration in fluid diet she began to have difficulty in passing water. This was followed by weakness in the legs, dropping of the wrists and weakness of the arms. Brandy was again resorted to as a stimulant. For a few days immediately prior to admission she had had diarrhœa. Mentally she had only become affected in the last few weeks of her illness; she had become forgetful, unreliable, and eventually drowsy. No history of pains could be obtained from the relatives. She had not had any serious illness before this and had borne four healthy children.

On examination the patient was found to be a pale, well-nourished female who was an unreliable historian of her own illness. She was edentulous, had a furred tongue and pale mucous membranes. The pupils were contracted, the right being larger than the left; both reacted to light and on accommodation. The fundi were normal. There was a divergent strabismus and on looking to the right or left a definite, though ill-sustained, nystagmus was present. The remaining cranial nerves were normal. There was definite wrist-drop on both sides with very marked weakness of the extensors and some weakness of the flexure of the wrist and fingers. The muscles of the fore-arm and arm were exceedingly tender to palpation. Below the elbow there was slight wasting of the muscles but no fibrillation was seen. The legs showed definite wasting, especially below the knee, which was associated with weakness of the muscles, more marked in the dorsiflexors than in the plantar flexors of the feet. The calves were exquisitely tender on deep palpation, and the skin and superficial tissues were tender up to the level of the umbilicus. All the deep tendon reflexes were absent even on reinforcement, except the right biceps reflex. The abdominal reflexes were absent; the plantar responses flexor. Sensation was difficult to test owing to patient's mentality, but there appeared to be some loss to superficial sensibility in both arms and legs, chiefly at the periphery.

The chest movements were normal and no clinical evidence was obtained of changes in the lungs. The heart was dilated, the apex-beat lying outside the mid-clavicular line. The heart sounds were normal. The liver was enlarged, three fingers' breadth below the costal margin, and was tender. The spleen was not palpable. There was no excessive pigmentation of the trunk or hyperkeratosis of the hands or feet. The urine contained a trace of albumin but no sugar or acetone.

During the three days which elapsed between admission and death, the temperature remained normal, the pulse-rate about 110 and the respiration rate at 20 to 26. At no time was any sugar found in the urine and tests for arsenic were negative. The patient's mental condition rapidly became worse until she was unable to answer any questions whatsoever. The condition of her nervous system remained the same until death.

After death the relatives furnished further details of the mental changes, which included forgetfulness, a tendency to uncleanliness and disregard for her personal appearance.

From the history, unsatisfactory though it was, together with the results of the clinical examination, a diagnosis of Korsakoff's syndrome was made.

A post-mortem examination was carried out by one of us (E. A. C.) within twenty-four hours of death.

The body was that of a well-nourished woman. The heart was surrounded by much sub-pericardial fat. The heart muscles looked pale, but except for dilatation of the left ventricle, the chambers and valves were normal. The aorta was covered with atheromatous patches, especially in the region of the arch. The liver was large, pale, coarsely cirrhotic, and on section obviously fatty. The spleen and kidneys were normal and no changes were observed in the suprarenal bodies. On removal of the brain and spinal cord no gross abnormality was observed. The cerebral blood-vessels appeared healthy. Portions of both sciatic nerves, both popliteal and internal tibial nerves were removed for section. Unfortunately no nerves were removed from the arms.

Microscopically, considerable changes were found in the internal organs as well as in the central and peripheral nervous system. The heart muscle showed fatty infiltration. In the aorta marked fatty changes were present in the intima, with definite atheromatous plaque formation. The vasa vasorum did not show any marked changes in their endothelium. The kidneys had slightly thickened capsules, but the glomeruli, the tubules and the blood-vessels all appeared normal. The spleen was mildly congested but did not exhibit any gross abnormality. The suprarenal bodies were normal. The liver showed a well-marked cirrhosis of the multilobular type; the liver tissue surrounded by fibrous bands was fatty, so that when stained with Scharlach R. the sections appeared to consist of masses of fatty substance. Scattered amongst the areas of fibrosis were small collections of round cells and in the immediate vicinity of the fibrous tissue new bile duct formation was evident.

Slices from the frontal, motor, parietal, occipital and temporal gyri were taken for microscopical examination. Portions of the mid-brain, pons, medulla and the corpus striatum were also sectioned. The changes in the frontal, parietal, occipital and temporal gyri were all similar. The most easily discernible abnormality was a fatty change in the endothelium of the small blood-vessels entering the cortex. There also appeared to be an excessive quantity of lipoid material which stained orange with Scharlach R. in the neuroglial cells immediately beneath the pia mater. These lipoid changes were more evident at the base of the sulci. The neuroglial cells appeared normal by Cajal's gold-sublimate impregnation method. No evidence was obtained that any alteration had taken place in the "sucker feet" attached to vessels with fatty endothelium. The nerve cells were apparently healthy as demonstrated by the following methods of staining: Scharlach R., Da Fano's neurofibril stain, and Nissl's stain. In the prefrontal cortex the white matter immediately subjacent in the cortex contained in several sections a larger number of compound granular corpuscles than are seen in normal brain tissues. The myelin, however, in sections stained by the Weigert-Pal method and by Scharlach R. appeared quite normal.

More interesting changes were found in the motor cortex. The Betz cells appeared as numerous as normal, but in many the nuclei were eccentric, whilst in others the lipoid material appeared excessive. In sections stained for Nissl granules an occasional cell was found in which the granules were arranged around the periphery. The neurofibrils appeared normal by Da Fano's method. The neuroglial elements were undisturbed by the pathological process, although immediately beneath the pia mater, as in the rest of the cortex, the neuroglial cells contained large quantities of lipoid material. The myelin appeared unaffected and there was no excess of compound granular corpuscles.

Sections from the corpus striatum showed no demonstrable lesion of the nerve cells of the thalamus, caudate, putamen or globus pallidus. The nerve cells of the thalamus adjacent to the ventricle appeared unduly laden with a fatty substance staining orange with Scharlach R., whilst in the subependymal region there was an excess of neuroglial cells containing lipoid material. In this region also a fair number of microglial cells were laden with fat. This suggested a degenerative process. In one section thrombosis of a small vessel was found, with some perivascular softening. This may have accounted for the fat-laden microglial cells seen in other sections. The neuroglia as well as the ependyma appeared normal. The choroid plexus exhibited fatty changes, the choroidal cells themselves containing fat globules, whilst the endothelium of the blood-vessels gave the reaction for fat with Scharlach R.

In the spinal cord maximal abnormalities were found in the cervical and lumbo-sacral enlargements. The anterior horns appeared to suffer most by the pathological process. The large anterior horn cells contained a large excess of fatty substance, and in many instances the fatty material lay outside the cell in its immediate neighbourhood. In such instances the nuclei were displaced eccentrically and the Nissl granules stained poorly and were grouped around the periphery. In the lumbar region many of the anterior horn cells had neither nuclei nor Nissl granules and only a faint outline of the cell was visible. Around these "ghost cells" there was no evidence of an acute reactive process. No changes were found in the posterior horns. The tracts of the spinal cord appeared normal when stained by the Scharlach R. and Weigert-Pal methods. Several pieces of the spinal cord were also examined by the Marchi-Busch method; in none of the sections examined by this method was there any evidence of early degenerative changes in the myelin. The anterior and posterior roots appeared normal by all staining methods. In some of the sections the endothelium of the smaller blood-vessels contained fat, but in no sections was a thrombosed vessel encountered.

Unfortunately the medulla, pons and mid-brain were damaged at the post-mortem. But in sections taken from various levels no changes could be demonstrated in the nerve tracts. The oculomotor nuclei were satisfactorily demonstrated and appeared normal; the lower cranial nerve nuclei were not demonstrated in the sections.

The following peripheral nerves were examined microscopically: Both sciatic nerves, both internal popliteal nerves and both anterior tibial nerves.

Definite degeneration of the anterior tibial and popliteal nerves was seen in sections stained with Scharlach R. The myelin sheaths, especially those of the larger nerve fibres, were broken up into globules which stained either intensely red or orange with Scharlach R. Similar sections stained by the Marchi-Busch method showed fatty changes, though these were not nearly so evident as with the Scharlach R. stain. Weigert-Pal sections showed obvious fragmentation of the myelin, but in no case complete demyelination. There was a similar degeneration, though of much lesser degree, in the sciatic nerves. In no section was there any evidence of an inflammatory reaction. No cellular infiltration of the nerves whatsoever was found. Pieces of the gastrocnemius and anterior tibial group of muscles were examined, but no abnormalities were detected.

DISCUSSION ON THE PATHOLOGY OF KORSAKOFF'S SYNDROME.

The lesions which we found in our five cases agree to some extent with those recorded by other observers. The changes in the nerves and in the spinal cord we do not propose to discuss in any detail as they present only the well-known features of a degenerative parenchymatous neuritis with consequent degeneration of anterior horn cells in the spinal cord. But even in the most chronic case, Case 2, in which symptoms of neuritis had been present for sixteen years, we could find no evidence of degeneration of any tracts in the spinal cord. Most of the cases hitherto recorded have shown degeneration of the posterior columns even with a history of short duration.

The lesions in the brain were confined to the cerebral cortex, except in Case 5, in which slight changes were present in the thalamus. The lesions were entirely incident upon the cells; no tract degeneration could be determined, but in the most chronic case there was slight atrophy of the most superficial tangential fibres in the frontal cortex.

The widespread deposit of lipochrome material in the nerve cells and neuroglial cells in the cortex was the most remarkable feature in our cases. This deposit has not, as far as we can trace in the literature, been described before in Korsakoff's syndrome. In three of our cases the lipochrome was particularly heaped up in the nerve cells of the prefrontal cortex. In one case the cells of the thalamus were loaded with lipoid. Deposits of lipochrome around blood-vessels and in their walls were common. In one case there was a gross fatty change in the endothelial lining of the cortical blood-vessels; in the other cases no changes could be seen in the walls of the vessels themselves, although heavy deposits of lipoid with many compound granular corpuscles surrounded them. This deposit of lipoid, which by solubility tests we have shown to be lipochrome, is not a specific lesion. Similar deposits occur in the nerve cells of senile patients and of patients dying from prolonged, exhausting diseases, but although we sectioned the brains of several senile patients and of patients who had developed psychoses during life, we could not demonstrate in them any accumulation of lipochrome in the neuroglial or microglial cells, nor was there such an amount present in the nerve cells as we found in our cases of Korsakoff's syndrome.

The only cases which we have been able to trace in which similar widespread deposits of lipochrome have been described are cases of pellagra. Kozowsky [16], in his review of the pathology of pellagra, drew attention to the enormous amount of yellow pigment he observed in the cortical nerve cells in Nissl preparations of the cortex. Winkelman [33] reported a series of cases of pellagra in which the chief pathological features were the accumulation of lipochrome in the nerve cells and glial cells of the cortex, especially in the frontal region, with fatty degeneration of the endothelium of the cortical vessels, a "primary degeneration" of the large Betz cells and a hyaline change in the walls of the blood-vessels in the cortex. Pentschew [27] confirmed these findings in his series, but was emphatic that they should not be considered specific.

There is some evidence that formation of excessive quantities of lipochrome is a disorder of cell metabolism. It is possible that in all these cases there is an exaggeration of the normal process of formation of lipochrome, which Marinesco [21] and Bertrand [2] have shown to be derived from the disintegration of the mitochondria; accumulation of the lipochrome in neuroglia and microglia may be the means by which transport of the excess of lipochrome is effected.

The chromatolytic changes which we observed in the nerve cells of the cerebral cortex, particularly in the Betz cells, are undoubtedly the same that Meyer [23], Cole [3], Mott [24], and other writers have described and to which Meyer gave the name "central neuritis." Meyer pointed out that these changes occur in the large pyramidal cells of the motor cortex in a high proportion of all cases of insanity, and that they are not peculiar to the syndrome of Korsakoff. Pearson [26], in a recent review of the whole subject of central neuritis, stated that he found the condition present in thirty-one brains out of a thousand examined consecutively. He observed chromatolysis only in the large and medium sized pyramidal cells of the motor cortex; it did not affect the prefrontal region or the smaller pyramidal cells as it did in our cases. The condition was present in many diseases other than diseases of the nervous system. Although in Pearson's series there were six cases in which alcohol was a toxic factor, in most of the other twenty-five it could be definitely excluded. Pellagra was the only disease in which chromatolysis of the Betz cells was found in every case. Pearson came to the conclusion that the changes in the nerve cells are due to a disturbance of cellular metabolism in which a toxin acting directly or indirectly on the nerve cells prevents the nucleus from extracting nutritive material from the tissue juices. The cell therefore exists on the cell chromatin; the nucleus migrates to the axon hillock in order that the part of the cell which transmits the impulses shall be preserved as long as possible. If the toxin acts for long enough the nucleus ceases to function and the cell dies. These results of metabolic disorder will produce the appearance of the cells seen in "central neuritis," a term which Pearson rightly regards as misleading, since there is no change in the axon; the condition is not, therefore, an "axonal reaction." Pearson suggested the term "primary cytolytic degeneration" for the process, a term which certainly conveys the true impression that the process obtains in the cell itself and is not consequent upon an extrácellular lesion of the neurone.

We are unable to confirm the observations of Marinesco [22] and Simchowitz [29], who found senile plaques in the cerebral cortex of patients who had had the Korsakoff syndrome. Marinesco's patient was aged 45, an age at which senile plaques do not occur except in advanced dementia. But Simchowitz's patient was aged 71, and she presented signs of dementia in addition to the psychosis associated with Korsakoff's syndrome, so that it is difficult to be sure that the plaques did not owe their existence to the presence of the condition of senile dementia.

We have already referred to our inability to demonstrate any tract degenerations in the spinal cord, even in the most long-standing of our cases. We can account for this absence of degeneration which so many others have observed only by postulating the selective action of the toxin in our particular cases.

From the histo-pathological examinations we have carried out we have evidence that in Korsakoff's syndrome certain changes in the nerve cells of the cerebral cortex occur in addition to the changes in the peripheral nerves which are those of a parenchymatous neuritis. The changes we found in the nerve cells were degenerative. They consisted in the deposition of the normal lipochrome pigment of the nerve cells in an excessive amount and in abnormal situations, such as the neuroglial and microglial cells, and around blood-vessels; and acute chromatolysis of the cortical nerve cells, especially of the Betz cells and of the larger pyramidal cells in the frontal region. Complete disintegration of nerve cells was rare, even in cases of long standing. Inflammatory changes were absent and the fibre tracts of the brain and spinal cord were intact. The chromatolytic changes in the nerve cells are not specific for Korsakoff's syndrome. As we have already pointed out, these changes may occur in many toxic states.

But except that we did not observe hyaline degeneration of the cortical blood-vessels the changes in the cortex which we have demonstrated in cases of Korsakoff's syndrome correspond exactly to those described in the cortex of patients dying from pellagra; this is evidence that these changes are specific neither for pellagra nor for Korsakoff's syndrome. Whilst it is obviously impossible to assign a common cause to the two conditions (which have however certain clinical features in common, in that in both a peripheral neuritis is accompanied by a psychosis), it is possible that a common factor may be present in the two conditions. This factor may be a "deficiency" which permits a toxin to exert its effects on the highly specialized nerve cells of the cortex.

SUMMARY.

(1) The ætiology of Korsakoff's syndrome and the criteria of nomenclature have been discussed.

(2) Five cases of Korsakoff's syndrome associated with alcoholism have been examined pathologically and the lesions found in the central nervous system have been described.

(3) The constant findings in the cerebral cortex were deposition of excessive amounts of lipochrome in all the nerve cells, in the neuroglial and microglial cells, and around the blood-vessels in the prefrontal and motor cortex, with acute chromatolytic changes in the larger nerve cells in these areas, especially in the Betz cells.

(4) The nature of these changes in the nerve cells has been discussed in relation to the question of a specific lesion in Korsakoff's syndrome.

(5) The view is expressed that the chromatolytic changes in the nerve cells is analogous to the appearances described by Meyer as "central neuritis."

(6) The similarity of the histo-pathological appearances between our cases of Korsakoff's syndrome and cases of pellagra has been remarked; both disorders show an enormous deposition of lipochrome in the cortical nerve cells, neuroglia and microglia at an age when normally lipochrome is present only in the nerve cells and in minute amounts, and also the central chromatolysis of nerve cells to which reference has already been made.

(7) The possibility is tentatively suggested that a common factor may operate in Korsakoff's syndrome and in pellagra, or that in these conditions there may be a deficiency in an essential factor, lack of which permits toxins to attack and damage the highly specialized nerve cells of the cerebral cortex.

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EPILEPSY AND GUNSHOT WOUNDS OF THE HEAD.

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THE frequency of occurrence of epilepsy after gunshot wounds of the head of all degrees of severity cannot be stated with accuracy, as statistics provided by medical observers are fallacious in that, for the most part, only those cases in need of treatment come under review.

Sargent [1] states that epilepsy had developed in 800 out of 18,000 cases of head wounds, that is, 4½ per cent. in 1920. At a later date, Bathe Rawling [2] traced 425 cases of head wound among whom 25 per cent. had developed "fits."

Wagstaffe [3] considers that fits are more common in proportion to the severity of the wound and where an organic lesion is present. Analysing 377 cases he found that the incidence of fits in the whole series, including concussion and fractured base without gunshot wound, was 10 per cent. whereas the incidence among those with penetrating wounds of the dura was 18 per cent. W. A. Turner [4] points out the important effect upon the estimate of the recognition of *petit mal* and epileptic equivalents which are so easily overlooked.

It was thought that inquiry at the present time would be likely to show a still higher percentage of traumatic epilepsy subsequent to gunshot wounds of the head, owing partly to the late development of epilepsy in a certain number of cases, and partly to the inclusion now of many cases of minor epilepsy not previously recognized as such. This, however, does not seem to be the case. A general survey of the official documents at the Ministry of Pensions in 17,300 cases of head wounds, the great majority of which are, of course, non-penetrating wounds, shows that epilepsy has been recorded as a second disability in only 270 cases. To these must be added head wounds with fits—not specifically diagnosed as epilepsy—and cases, fully pensioned, in which no claim for an additional disability has been made. Sargent's 800 cases probably include cases in which fits occurred at the time of being wounded, but in which an established and permanent epilepsy did not ensue. Allowing for these sources of error, it is probable that the percentage given by Sargent is still a fairly correct estimate. The incidence of epilepsy in severe and penetrating head wounds must of course be much higher, but exact figures are not available.

It was at one time generally held that traumatic epilepsy develops within a few months of injury, and that a direct connection between injury of the head and subsequent "fits" could not be assumed unless the intervening period was comparatively short. In the majority of cases, especially of superficial wounds, this is no doubt true, but many authentic cases of epilepsy undoubtedly due to, but supervening years after, trauma of the head have been recorded. The mechanism operating in the late development of traumatic epilepsy is probably, as Sargent has suggested, the formation of adhesions, scar tissue and resultant drag. Foerster and Penfield [5] deal with the question of the scar traction on and in the brain in the development of traumatic epilepsy. These changes not only relate to the scar but also produce a marked dilatation and displacement of the ventricle in association with hydrocephalus. They consider this dilatation and displacement of the ventricle as due to scar traction which passes from the scar deeply through the scar-changed brain to the ventricle.

In Wagstaffe's series, the longest interval was seven and a half years. In the series upon which the present article is based, there are eleven cases in which ten years or more intervened between the trauma and the onset of definite epilepsy. The longest interval is fourteen years. It appears probable, however, that the majority of these cases belong to the group of unrecognized epileptics, and it must be very rare for epilepsy to develop a long time after the inducing trauma without warning such as vertigo, paroxysmal headache, short periods of "absent-mindedness," &c.

In most of the cases now under consideration, during the interval there had been frequent attacks of vertigo, and this, as is pointed out later, must be looked upon as probably an epileptic symptom. Nevertheless there are cases in which vertigo persists without the development of epilepsy, and it is a question whether the diagnosis of epilepsy on the presence of vertigo alone is justified. On the other hand, some few cases may develop epilepsy after a long period during which there is in fact no premonitory vertigo.

In Case 12 of this series, careful inquiry failed to elicit a history of vertigo or any other warning symptom. The wound was sustained in August, 1916, there was temporary hemiparesis which soon cleared up, and the patient was entirely free from symptoms till July, 1930, when he had a fit while at work, and he has since had two more. In Case 39—

wounded in 1916—the vertigo had been very infrequent and slight, and would not have demanded attention had not two fits occurred in 1929. In passing, it may be noted that in both these cases there was an intracranial foreign body. In Case 19, wounded in 1914, vertigo commenced nine years after the wound and the first actual fit occurred in 1926. He is now the subject of frequent major fits.

During the past twelve months, 84 cases of old gunshot wounds of the head have been treated in this hospital, and observation has been specially directed to the occurrence of epilepsy and mental deterioration, and the inter-relation between these two conditions. All the cases have had definite trauma of the head, but the degree varies within wide limits. They are therefore divided into two main groups: (1) Those showing definite evidence by palpation, or by X-ray, of severe trauma, e.g., gap in bone, metallic foreign bodies or fragments of bone in the cranial cavity. These comprise 54 cases. (2) Those with a definite history of gunshot wound of the head, but now showing no gross structural change resulting from this. These comprise 30 cases.

Of the 54 cases of penetrating wounds, 40 were subject to major epilepsy, or major and minor epilepsy combined, 3 had attacks of *petit mal* only; in 1 case there were Jacksonian attacks only, in 5 vertigo only, and in 5 cases the attacks consisted of emotional outbursts only and are described as "functional."

Of 30 superficial wounds of the head, 7 had major epilepsy, 5 had only *petit mal*, 4 suffered from vertigo only, 7 had only hysterical attacks, 1 case had Jacksonian fits confined to the right leg, and 6 cases were not diagnosed owing to absence of fits while in hospital, and the doubtful nature of the other evidence submitted.

Of the 84 cases under consideration, therefore, 57 were definitely epileptic (including 2 cases of Jacksonian epilepsy), 9 had vertiginous attacks which were probably closely related to *petit mal*, 12 had emotional outbursts which may be looked upon in some cases as hysterical, but in others were epileptic equivalents, and 6 cases were not diagnosed.

Vertigo.—The persistence of vertigo in gunshot wound of the head is of great importance in prognosis. Nearly all cases of delayed traumatic epilepsy are characterized by frequent attacks of vertigo during the years intervening between the gunshot wound and the onset of epilepsy. Such vertigo seems to be closely allied to minor epilepsy, and tends to become more severe as time goes on, until it may be accompanied by transient loss of consciousness. In some cases of vertigo, major epilepsy does not ensue, but the vertiginous attacks assume an epileptic type. They are accompanied or followed by slight mental confusion and symptoms of vaso-motor disturbance, pallor, flushing, sweating, &c. Chartier [6] has described such attacks under the name of "Reflex Vertigo."

"*Functional*" *attacks*.—These are characterized by loss of emotional control. There is no loss of consciousness, no true vertigo, and but little confusion. They tend, usually, to be longer in duration than attacks of vertigo and *petit mal*, but this is not always the case. In some cases there is irregular jactitation, in others resistiveness or apparently purposeless violence.

Epileptic equivalents.—Epileptic equivalents are met with in traumatic, though probably not so frequently, as in idiopathic epilepsy. In several cases of this series emotional outbursts replaced, or alternated with, major epileptic fits. Wandering and automatism associated with *petit mal* occurred in three cases. Two cases of so-called procursive epilepsy were noted, in which sometimes before a fit the patient would run about in an automatic or confused way.

In the absence of major attacks, equivalents present difficulties of diagnosis. They have to be distinguished from hysterical manifestations; for equivalents, dreamy states, periodic depression, are symptoms of a permanent mental change. The question arises whether the occurrence of equivalents points to "predisposition." Feuchtwanger, quoted by Peritz, concludes that, when a large group of cases is considered, epilepsy following brain damage shows in its clinical picture all the symptoms which are also seen in genuine epilepsy; attacks, aura, giddy states, periodic depression, minor attacks, absences, dreamy states, confusional states, dementia, alterations of character and disposition. In the individual case there is no symptom which, from its manifestation alone—e.g., equivalent, alteration of personality, &c.—allows of conclusions as to an "epileptic predisposition" or "latent epilepsy."

The occurrence of equivalents and mental changes observed in the group of cases on which the present article is based is in conformity with the conclusions quoted above.

As regards skull injury in which brain injury is uncertain, though equivalents in themselves cannot be regarded as argument in the sense of a predisposed genuine epilepsy as against a traumatic, occurring in conjunction with other factors—e.g., psychopathic heredity, alcoholism, pretraumatic instability, &c.—they would support the argument of epileptic predisposition.

Jacksonian epilepsy.—Jacksonian epilepsy is now rarely met with among pensioners with head wounds, although in a few cases the fits tend to be localized or more marked on one side than the other. In some cases there is a history of Jacksonian epilepsy occurring shortly after the wound, ceasing for a time and being succeeded, perhaps years later, by generalized major epilepsy. A history of Jacksonian epilepsy is not, however, to be relied on, as the term, "Jacksonian epilepsy," appears to have been used often loosely as synonymous with traumatic epilepsy.

Adie and Wagstaffe [8] state that cases with localized fits at the time of the wound are not more liable than others to develop subsequent traumatic epilepsy.

Wagstaffe appears to have revised this opinion, for, writing at a later date, he states that traumatic epilepsy appears to be much more common in those cases which developed transient Jacksonian fits within a few days of the injury.

Among this series there were only two cases of Jacksonian epilepsy. In both cases the wound was situated exactly over the upper end of the left central sulcus. The seizures were limited to the right leg, there was not complete loss of consciousness, and in one case there was wasting of the leg.

Mental deterioration.—In relation to mental deterioration, two factors were investigated: the type and frequency of the fits, and the site and severity of the head wound. Of these two factors, the first appears to be the more important, although the latter is not without its effect. Of severe head wounds, 40 out of 54 showed some degree of mental deterioration, i.e., about 75 per cent. Of those with less severe wounds, 13 out of 30 showed some deterioration, i.e., about 43 per cent. Of 17 cases of severe trauma with frequent fits, all were mentally deteriorated in some degree, i.e., 100 per cent. Of 37 cases of severe trauma with infrequent fits, or functional or vertiginous attacks only, 23 were deteriorated, i.e., 62 per cent.

In Table I these figures are compared with 108 cases of idiopathic epilepsy in whom mental deterioration was present in 94 per cent. of those with frequent fits, and in 47 per cent. of those with infrequent fits. Superficial wounds of the head show less deterioration than idiopathic epilepsy, because they include cases which are not in fact epileptic.

Site of wound.—(1) Anterior to, and not involving, the motor cortex. In twelve out of fifty-four cases of severe gunshot wound, the damage appeared to be limited to the anterior frontal areas.

The characteristics of trauma limited to the prefrontal areas are infrequency of fits, absence of aura, impairment of memory with a peculiar alteration of emotional tone, and in many cases a long latent period between the trauma and the onset of epilepsy. The average period between the infliction of trauma and the onset of epilepsy in these twelve cases is over six years; the longest period is fourteen years. This latent period, however, in nearly every case is characterized by vertigo and frequent headache.

TABLE I.—INCIDENCE OF MENTAL DETERIORATION IN IDIOPATHIC AND TRAUMATIC EPILEPSY.

		No impairment	Emotionally unstable without intellectual deterioration	Slightly deteriorated	Moderately deteriorated	Severe deterioration	Deterioration
Frequent fits (more than 24 major attacks a year or 12 minor monthly)	Consequent upon severe GSW head	—	—	7	5	5	100 %
	Subsequent to superficial GSW head	—	—	1	—	—	—
	Idiopathic ..	1	3	21	25	18	94 %
Infrequent fits including also vertigo only or "functional" attacks only	Consequent upon severe GSW head	10	4	11	11	1	62 %
	Subsequent to superficial GSW head	10	7	8	4	—	41 %
	Idiopathic ..	12	7	12	8	1	52 %

When the trauma is strictly limited to the anterior frontal area there is complete absence of aura, and, when the fits are diurnal, this lack of warning involves danger from sudden falls. The wearing of a suitable head-shield is therefore often necessary. Where an aura exists with a frontal injury, full investigation will always reveal an additional area of trauma. For example, in Cases 46 and 47, though the main site of trauma was at the frontal pole, a gustatory aura was complained of. Full investigation left little doubt that the temporal lobe was also damaged. Where the damage tends to encroach on the motor area of the cortex, as is to be expected, a motor aura is often found. This may be very limited, e.g., a rotation and fixation of the head, and serve as a quite inadequate warning to the patient.

When fits occur in purely frontal injuries they are comparatively infrequent, usually of major type, and well spaced, that is to say, the intervals between fits are long, two or three months or more, and there is little or no tendency for the fits to group. Status epilepticus, in my experience, is very rare in traumatic epilepsy where the injury is strictly limited to the anterior frontal region.

Of these 12 cases, one had had only 3 fits in all; of the other 11 cases, the average number of fits per year was 14. In 7 cases the fits were of major type only, in 3 cases *petit mal* and *grand mal* both occurred, and in 2 cases there were only attacks of vertigo and possibly *petit mal.*

An alteration of emotional tone peculiar to injury of the frontal region was observed. This consists in emotional dulling, with a loss of interests in general, combined with a certain peevishness and irritability when in any way restricted or interfered with. There is, as it were, a loss of capacity for normal enjoyment and pleasure, and at the same time a centring on self, leading to irritability and impatience with others. The memory is usually more or less impaired, but intellectual enfeeblement does not proceed so rapidly or so far as in those cases of traumatic epilepsy in which the fits are more frequent, and especially in those in which the fits tend to group. In two cases of this sub-group there was no apparent defect of memory or of emotional control; one of these had only three major fits in all, and the other had only infrequent *petit mal.*

Motor or sensory defects do not occur when the injury is limited to the prefrontal area, but impairment of stereognostic sense was found in two cases, though the injury seemed to be definitely limited to the area under discussion.

(2) Trauma involving the motor cortex. In twenty-three of the fifty-four cases of severe trauma, the motor cortex was involved. As would be expected, a motor aura is usual in such cases, but this is often of such short duration as to afford no adequate warning. The interval between the wound and the onset of epilepsy is noticeably shorter than in trauma of the other cerebral areas. Most of these cases developed epilepsy within a few months of being wounded, and, where in a few cases there is an apparently long latent period, inquiry generally produced a history of vertigo, mental blanks, &c.

In most cases of traumatic epilepsy, when the motor cortex is involved the fits are of major type, tend to become more frequent with the passage of time, and tend to group, so that status epilepticus is not uncommon. Of the 23 cases, 12 were the subject of very frequent major and minor attacks, 4 had major epileptic fits about once a month, 2 had very infrequent major fits and occasional epileptic equivalents, 3 had very rare major fits with frequent vertigo or *petit mal;* one case suffered from occasional vertigo, but had never had a definite epileptic attack, and one case had functional attacks (emotional outbursts) only.

Mental deterioration is marked in this group, and not infrequently psychoses, temporary or permanent, develop. Most often the psychosis takes the form of a more or less transient mania and confusion, but stupor and hallucinational and delusional forms have been observed. Where damage of the anterior frontal areas is added to that of the motor cortex, there is a slowly progressive dementia, emotional dulling and apathy, gradually replacing emotional instability and tendency to mania.

Epileptic equivalents were noted in two cases of this group. In one case (No. 32), wandering in a state of fugue occurred occasionally in the intervals between major epileptic fits. In the other case (No. 28), outbursts of uncontrollable weeping or emotional excitement have to a large extent replaced fits formerly of generalized major type with a motor aura of the left hand and face.

Various degrees of paresis, varying from complete cortical hemiplegia to subjective sensations of weakness, are found in this group. These tend to improve, but it is seldom that some residual sign of lesion of the motor path, such as a Babinski reflex, cannot be found.

(3) Injuries posterior to the motor cortex. In ten cases in which the trauma was entirely posterior to the motor cortex, the most noticeable feature was the infrequency of fits. In three of these cases fits have now ceased, and are represented only by periodic unreasonable and uncontrollable emotional outbursts. In four other cases there have been only six major fits or less all told. Aura was absent except in two cases (Nos. 36 and 40). In one of these there was a visual aura, consisting of flashes of light and hemianopsia for a quarter of an hour before the fit, and not infrequently this aura occurred without a fit ensuing. Byrom Bramwell [8] has described a similar condition occurring in tumour of the occipital lobe under the picturesque name of Visual Jacksonian attacks. In the other case there was sometimes a visual, sometimes an auditory aura. Three of this group showed no mental deterioration, and in the others the degree of deterioration was slight. In one case (No. 45), the cerebellum was peppered with numerous small metallic foreign bodies, but none of the classical signs of cerebellar lesion was present.

(4) Injuries involving the temporal lobe. In six cases the main trauma appeared to have fallen on the temporal lobe, usually in association with damage to the frontal or the parietal cortex. In two

of these cases the fits were all of minor type, but were associated with automatism and epileptic equivalents, and in four cases both major and minor fits occurred, were rather frequent and tended to group. In three cases, fits associated with a gustatory aura were noticeably prone to occur at meal times.

Four out of these six cases showed marked mental deterioration. The other two cases, though not deteriorated, were liable to confusion and automatism after fits.

One case (No. 47) developed *petit mal* with an aura of nausea eleven years after being wounded. During the "latent period," however, he had had periodic attacks of unexplained nausea and vomiting. It is possible that this nausea and vomiting were actually an aura without subsequent fit, or there may have been *petit mal* of such short duration as to escape notice. In this case both frontal lobes had been damaged and there was a foreign body in the left temporal pole.

(5) In three cases the bullet had entered anteriorly and had been extracted from the posterior part of the brain, so that it was not possible to localize the main seat of trauma. In all these cases the mental deterioration was marked. In two the fits were frequent, and in the third, though actual fits were few, there was frequent severe vertigo.

Superficial wounds.—It is admitted that the degree of cerebral injury cannot be estimated by the extent of the wound and injury of the skull. Nevertheless my experience of these cases leads me to believe that "epileptic predisposition," or "nervous instability" plays a larger part in the production of "fits" in those with superficial wounds than in those with deep and permanent trauma. Cases of epilepsy associated with painful superficial scars have been described under the term "reflex epilepsy," and Oppenheim [9] has called attention in particular to this cause of epilepsy following cranial injuries. All cases of this kind which have come under my observation have proved on investigation to be "functional," not epileptic. The stimulation of such a scar by handling serves to revive a painful effect associated with the original trauma and induces an emotional outburst sometimes accompanied by some degree of dissociation.

In the great majority of scalp wounds, the fits, whether "functional" or epileptic, are the result of shock, fear, or other emotion reacting upon an unstable nervous system, and are not due to structural damage or direct irritation by cicatrices, adherent dura, &c. Such fits supervene within a short period of the injury, but a permanent epileptic or "epileptoid" condition may be established.

Table II.—Frequency of Fits in Relation to Site of Injury.

	Frequent	Infrequent	Minor only	Vertigo only	Functional	Total
Frontal—not involving motor cortex	3	8	—	1	—	12
Involving motor cortex	12	9	—	1	1	23
Posterior to motor cortex	3	4	—	—	3	10
Involving temporal lobe	4	—	2	—	—	6
Traversing wounds	2	—	—	1	—	3

Of the thirteen cases in which a definite diagnosis of epilepsy could be made, one has Jacksonian attacks limited to the right leg, and accompanied by transitory confusion. These attacks commenced nine years after being wounded, though there had been complaint during the interval of weakness and numbness or pain in the leg. The scar is situated over the upper end of the left central sulcus, but X-rays show no evidence of damage to the bone. In another case there was a "latent period" of seven years, which, except for headache, was devoid of symptoms. Definite minor epilepsy was observed during this patient's residence in hospital, and he was stated to have had infrequent major fits at home. In two cases of superficial temporo-frontal injury, five years elapsed from the date of the wound to the onset of epilepsy. In eight cases epilepsy commenced within a few months of injury. In other cases there were claims for epilepsy after long latent periods, but a positive diagnosis was not possible owing to the absence of fits, or even of vertigo, while under observation in hospital.

Seven of this group were considered to be definitely hysteric, not epileptic.

Conclusions.

The term "traumatic epilepsy" should be limited to cases of epilepsy resulting from injury to the brain or its membranes. The term "Jacksonian epilepsy" should be applied only to localized fits of cortical origin.

Traumatic epilepsy may develop as late as ten years or more after severe injury of the head, but usually there has been in the interval vertigo, paroxysmal headache, or other premonitory symptoms. Epilepsy following superficial wounds of the head is most often psychogenetic in origin. The fits in such cases are the result of shock, fear, or other emotion reacting upon an unstable nervous system, and are not due to structural damage or direct irritation by cicatrices, &c. Such epilepsy supervenes within a short period of the injury.

The fits in traumatic epilepsy are, in most cases, clinically the same as in idiopathic epilepsy. Both major and minor attacks occur. In severe gunshot wound of the head there are, however, certain variations in the type of subsequent epilepsy. These variations, though not absolute, are sufficient to form a basis for differentiation, and an aid in diagnosis. They depend upon whether the trauma involves the motor cortex, or whether it is mainly anterior or posterior thereto. Epilepsies following lesions of the temporal lobe have also their local signs. These differences are mainly observed in penetrating wounds, but may serve, in superficial lesions, to distinguish a true traumatic epilepsy from an epiplepsy of psychogenetic origin. When there has been a long latent period, with complete freedom from symptoms, more recent possible cause of epilepsy must be excluded before the epilepsy can be considered of traumatic origin.

Vertigo is more common in traumatic than in idiopathic epilepsy, and in some cases may be the only epileptiform symptom. In other cases it may precede the onset of definite epileptic attacks by many years.

Mental deterioration is more rapid in traumatic than in idiopathic epilepsy. It is related mainly to the frequency of the fits, but, when fits are infrequent, deterioration is more rapid and marked in severe wounds of the head than in idiopathic epilepsy with a similar frequency of fits.

I desire to express my thanks to the Director General of Medical Services of the Ministry of Pensions for permission to publish this article.

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FACTORS DETERMINING THE DIFFERENTIATION OF THE CEREBRAL CORTEX IN SEA-LIVING MAMMALS (THE CETACEA). A STUDY OF THE BRAIN OF THE PORPOISE, TURSIOPS TRUNCATUS.

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COMPARATIVE neurological studies of the common vertebrates have furnished illuminating data concerning the phylogenetic development of the cerebral cortex. Into the anterior portion of the neural axis, which was at first dominated by the olfactory nerve, other types of sensory impulses have penetrated. Perhaps the first to reach this region were trigeminal, carrying impulses from the snout and the sinus hairs; optic, acoustic and fibres from cutaneous and deep structures of the body eventually reached the cortex and developed end-stations there. Around these projection areas other portions of the cortex were differentiated for the correlation of these stimuli. This neocortex developed in the dorsal portion of the old olfactory pallium, and with its further growth the older olfactory cortex was pushed to the mesial and lateral surfaces of the hemispheres.

If the story of the phylogenetic development of the central nervous system is followed, it will be realized that there have been other attempts to develop dominant correlation centres in the cephalic portions of the neural axis. In lower vertebrates, perhaps reaching their highest relative development in birds, the optic end-stations in the roof of the mid-brain were of great importance. The cells became arranged in a laminated pattern, similar to that developed in the cerebral and cerebellar cortices. Other types of sensory fibres were attracted into this region, in particular the acoustic fibres. But this correlation centre did not flourish and has undergone regression in mammals. This is perhaps due to the fact that there is tendency for dominance in the most cephalic portion of the neural axis. Dr. Adolf Meyer has called the roof of the mid-brain an archæological museum.

The cerebral cortex, however, has undergone extremely rapid growth and differentiation in Primates, culminating in the fore-brain cortex of man; again, comparative neurologists have speculated concerning the contributing factors. Many investigators believe that, in this case, influences from the visual apparatus played a dominant part. With the regression in size of the snout and the movement of the eyes to the front of the head, binocular stereoscopic vision became possible. This gave a certain depth and perspective to objects in the environment. With the acquisition of this better perspective by the animal the fore-legs began to be utilized for seizing food and climbing in the trees, and were more and more freed from their function as locomotor props. The cerebral cortex, under the influence of afferent impulses from the eyes, thus came, in time, to control the finer co-ordinated movements of the hands.

A sharp contrast to this story is the history of the evolution of the cerebral cortex of the Cetacea. These mammals present an interesting history of adaptation. After they had reached a stage of development comparable to that of the Carnivora (cat and dog) they became adapted to a life in the water. This produced marked changes in all portions of the body, including the central nervous system. In the adjustment to an aquatic environment the hind-leg was lost, so that only minute vestigial remains are found within the body of the porpoise. The fore-leg, likewise, underwent a marked reduction, changing its conformation and becoming the flapper. The tail developed into a powerful muscular appendage, supplemented by the growth of caudal flukes, highly adapted to locomotion in the water. The skin has become thick, smooth and hairless, and has lost its sweat, as well as sebaceous, glands. The pinna of the ear has been lost and the external auditory meatus reduced. Furthermore, the eyes and the eyelids have undergone pronounced modifications. Many of these changes upon the surface have been brought about to further the ease of gliding through the water.

The author had the opportunity a few years ago of visiting a porpoise fishery off the coast of North Carolina with a group of workers interested in this unique animal. Six young adult males, each 8 ft. long and weighing about 800 lb., were caught upon a single morning. It had been hoped that certain physiological studies relative to the nervous system could be made at the fishery. For example, it was planned to stimulate the cerebral cortex with a faradic current and also to produce decerebrate preparations. These experiments were largely unsuccessful, due to technical difficulties. However, the brains were removed and carried to Baltimore for further study. Both macroscopic and microscopic examinations were made; through the kindness of Dr. Adolf Meyer several serial sets of sections were stained by the Weigert-Pal technique. A detailed report of the findings is published in another place. The drawings that illustrate this paper were made by Mr. James Didusch of the Carnegie Institution of Washington.

When the central nervous system of the porpoise is examined, it is found that the cerebral cortex is very large and well differentiated. The lateral surface of the brain is shown in fig. 1, and it is at once clear that the pattern of convolutions is even more complicated than that observed in man. Structural changes in the shape of the skull have had an effect on the conformation of the cranial cavity and of the brain. A marked foreshortening of the skull has occurred, brought about by telescoping of this structure, so that the frontal and occipital bones override the parietal bones, producing a cranial cavity which is deep and wide but relatively short antero-posteriorly. The blow-hole, a complex naso-pharyngeal structure adapted to the regulation of intake and escape of air, has developed anterior to the cranial vault. With the formation of the blow-hole mechanism, the nostrils have shifted to the dorsum of the head.

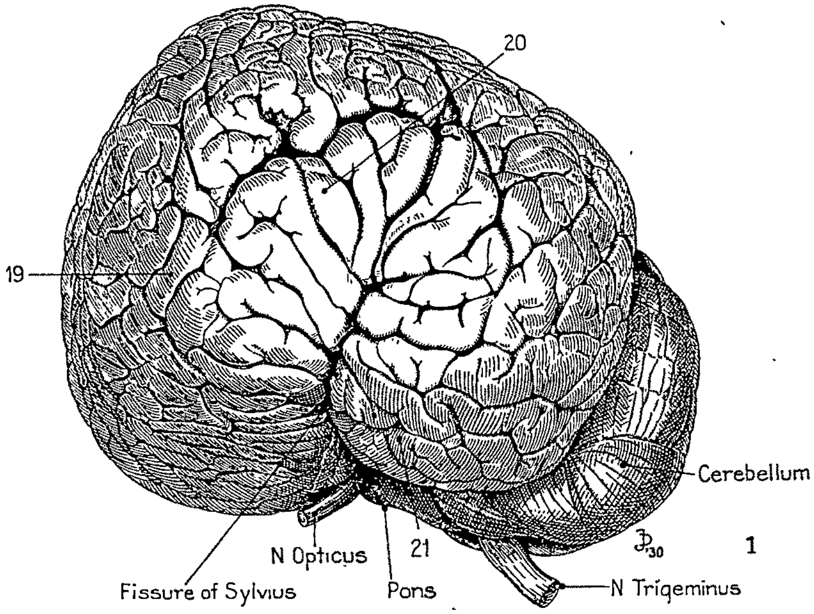


FIG. 1.—Drawing of lateral surface of the cerebral cortex of the porpoise.

These changes are all mirrored in the brain, which is wide laterally and foreshortened antero-posteriorly. The frontal surface is flat, rising abruptly from its ventral to its dorsal surface. Since the skull has been flattened anteriorly to leave room for the blow-hole mechanism, considerable rotation of the fore-brain has occurred. This causes the fissure of Sylvius to extend in a vertical rather than a horizontal plane (fig. 1).

The occipital lobe is not large; the temporal lobe is a conspicuous portion of the cerebral cortex. Former investigators have suggested that the shape of the fore-brain was determined by the absence of olfactory nerves or nuclei; undoubtedly the mechanical factors just mentioned are much more important.

The fissure of Sylvius may be identified in fig. 1. A number of gyri radiate from this fissure. These are bounded laterally by a semilunar fissure, the supra-Sylvian fissure. A number of previous workers have studied the pattern of gyri and sulci in the cortex of the porpoise and have attempted to homologize them with those found in other mammals, particularly carnivora. The present study endeavoured instead to determine the types of sensory fibres reaching the cerebral cortex and to localize the primary projection and correlation centres there.

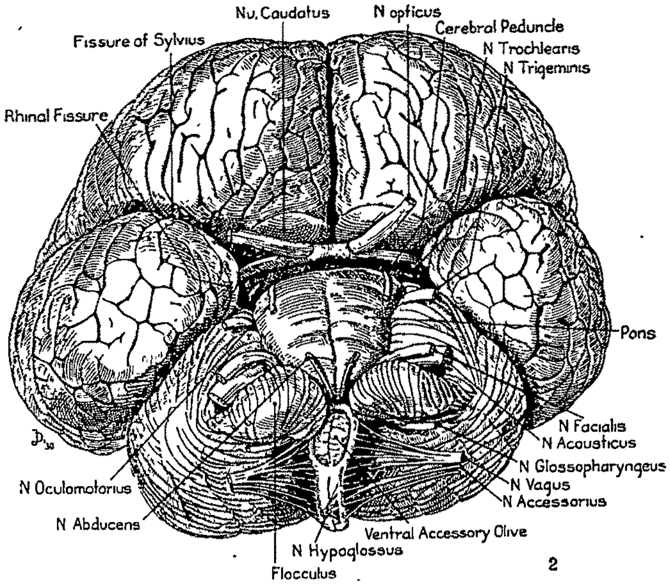


FIG. 2.—Ventral view of porpoise brain.

The ventral surface of the porpoise brain is pictured in fig. 2. The caudate nuclei lie on the surface of the brain at the ventral edge of the frontal lobes. The rhinal fissure may be identified at the very tip of the temporal lobe. The great width of the fore-brain is evident from this drawing.

The cerebellum is very large (figs. 1 and 2) and consists of two large hemispheres with a small vermis squeezed between them. The conspicuous flocculus is characteristic of all water-living mammals. It is also evident that the connections of the cerebral with the cerebellar hemispheres are well developed inasmuch as the pons is so conspicuous.

This drawing of the ventral surface of the brain shows (fig. 2) the cranial nerves. No remnants of olfactory nerves or olfactory bulbs were found in any of the six brains examined. It is probable that all the optic fibres cross in the chiasma and reach the opposite thalamus. The oculomotor, trochlear and abducens nerves are not remarkable. The trigeminal nerve is well developed; the ophthalmic branch is greatly diminished in size, but the maxillary and mandibular are large. The facial nerve is particularly differentiated in that it innervates the complicated musculature of the blow-hole apparatus. The acoustic nerve is very large and it is the cochlear portion which shows the greatest development. The glossopharyngeal, vagus, accessory and hypoglossal nerves are not remarkable.

The present paper is concerned with the factors contributing to the great differentiation of the cerebral cortex in the porpoise; the gross and microscopic structure of the nervous system has been described at some length in another paper (Langworthy, 1931). Perhaps the first step is to determine the relative development of pathways carrying sensory impulses to the cerebrum.

The fore-brain is fundamentally an olfactory end-station, but no olfactory nerves or olfactory bulbs were present in the six porpoise brains examined. The olfactory correlation cells and tracts were either absent or greatly reduced in size. This was also found by Addison (1913) in studying the rhinencephalon of the dolphin (*Delphinus delphis*). The olfactory cortex at the base of the frontal lobe is absent in the porpoise and the head of the caudate nucleus projects on the ventral surface of the brain. The parolfactory area is represented and gives rise to the stria medullaris and stria semicircularis. All of these structures are of small size. The hippocampus is very diminutive, as is also the fornix which ends in a small group of cells, the mammillary body. From the mammillary body a tenuous tract goes to the anterior nucleus of the thalamus. The mammillary body cannot be distinguished macroscopically on the ventral surface of the brain. No tracts can be followed to the hippocampus major. The anterior commissure was not identified. The presence of the parolfactory area and hippocampus major, although diminished in size, suggests that they have other than olfactory connections. Edinger believed that the parolfactory area is the centre for an oral or snout sense mediated largely by the trigeminal nerve. It is clear, therefore, that no olfactory nerve fibres enter the central nervous system of the porpoise and the olfactory nuclei in the fore-brain are greatly reduced in size.

Sections of the spinal cord were examined to localize pathways carrying afferent impulses from the cutaneous and deep structures of the body to the thalamus and cortex. The anterior horns of the gray matter are large and contain numerous motor cells arranged in groups or clusters. The posterior horns, on the other hand, are rather small. The ventral roots of the spinal cord appear to be larger and to contain many more fibres than the dorsal. The ventral tracts of the cord are differentiated out of all proportion to the lateral and dorsal tracts. It is probable that the anterior columns contain many short intersegmental fibres, correlating the activity of the musculature. The posterior columns are fairly large and may be divided, in the upper portion of the cord, into gracilis and cuneatus tracts. The fibres of the posterior columns end around the cells of the posterior column nuclei in the medulla; the medial lemnisci are fairly developed and may be followed to the thalamus. In this way impulses from the muscles must eventually be relayed to the cerebral cortex. In proportion to the bulk of the striated musculature and the delicate co-ordination of movements, this pathway carrying afferent impulses from the muscles to the cortex is small.

The skin of the porpoise is so thick that it is not adapted to the reception of delicate shades of stimuli. There are probably few and poorly differentiated cutaneous sensory nerve endings. The pain-temperature tract or spino-thalamic tract is very small.

The trigeminal nerve carries stimuli to the central nervous system from the region of the head. Again cutaneous sensation must be decreased in the porpoise, but the naso-pharynx probably contains numbers of sense organs. The sensory nuclei of the trigeminal in the medulla have all been identified but they are of relatively small size. Trigeminal stimuli have played little part in the development of the cerebral cortex.

The importance of the optic nerve in the differentiation and rapid growth of the cerebral cortex in higher mammals has already been emphasized. In the porpoise, however, the optic bulbs are placed so far laterally upon the head that binocular stereoscopic vision is impossible. Moreover, it has been clearly shown by one observer that, in the dolphin at least, all the optic fibres decussate in the midline so that there are no arrangements in the central nervous system for anything more complicated than panoramic vision. The optic end-stations in the roof of the mid-brain and in the thalamus are small. Although optic fibres reach the cerebral cortex they can scarcely have played a prominent part in its unusual growth.

The optic nerve is indicated in fig. 1 and the chiasma in fig. 2. The optic colliculi in the roof of the mid-brain are much smaller than the acoustic (fig. 3). This proportion is reversed in other groups of mammals. Moreover, in fig. 3 the acoustic geniculates are large; the optic geniculates can scarcely be discerned and appear only as small swellings in the course of the optic tracts.

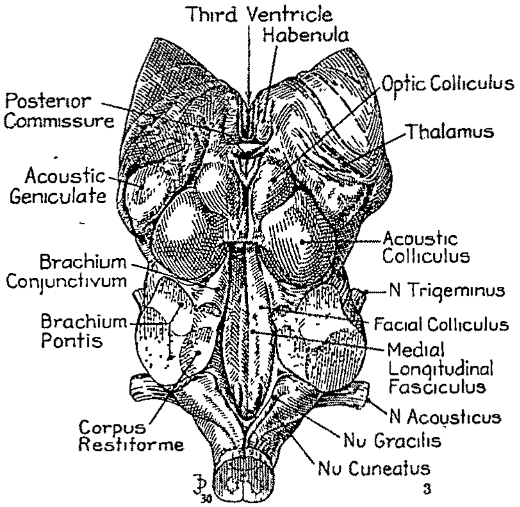


FIG. 3.—Dorsal surface of the brain-stem of the porpoise, to show particularly the acoustic colliculi and acoustic geniculates.

The acoustic nerve, on the other hand, is very large. Examination shows that it is the cochlear and not the vestibular portion that is of great size. The vestibular nerve compares favourably in size with the other sensory components already discussed; the cochlear nerve far surpasses them. Moreover, the acoustic connections in the brain are the conspicuous landmarks both on macroscopic and miscroscopic examination.

There is no evidence at the present time that the sense of hearing is particularly acute in the porpoise. It must be remembered in this connection that the acoustic apparatus had to be completely reorganized for use in a fluid media. It may be due to this functional adaptation that the cochlear mechanism has hypertrophied. It is remotely possible that the cochlear portion of the nerve has taken over the function of controlling equilibrium in the porpoise.

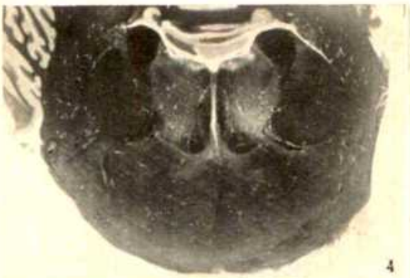
The cochlear nerve is seen in fig. 2; the acoustic colliculi and geniculates in fig. 3. The acoustic colliculi lie further from the midline and are larger than the optic. They are connected across the midline by a commissure of fibres. There is another peculiarity of the acoustic geniculates in addition to their size, for, in the porpoise, they do not present a smooth surface but are thrown into folds and ridges. This demonstrates the marked expansion and development of this region; perhaps it represents an attempt to supply nutrition to a larger area, utilizing the blood supply already present. The marked unfolding of the cerebral and cerebellar hemispheres, characteristic of certain mammals, may be an adaptation to produce adequate vascularization.

Photomicrographs of the brain demonstrate the acoustic connections. Fig. 9 shows a transverse section through the brain-stem at the level of the acoustic nerves. The great size of the cerebellum is also evident; the hemispheres are particularly well developed while the vermis is squeezed into the dorsal midline. The flocculi project beneath the ventral surface of the brain-stem. The contour of the dentate nuclei of the cerebellum is characteristic; in most mammals with large cerebellar hemispheres the dentate nuclei are markedly convoluted, while here they form an almost solid mass of cells.

Another transverse section through the cerebellum shows the acoustic lemnisci (fig. 10). These fibre tracts are associated on their mesial surfaces with a conspicuous mass of cells, the nuclei of the acoustic lemnisci which are white in the photomicrograph. The pons lies ventral to the acoustic tracts. The brachia conjunctiva, consisting largely of efferent fibres from the cerebellum, projects into the fourth ventricle.

The large size of the pons is shown more clearly in fig. 4. The two dark groups of fibres just ventral to the fourth ventricle form the brachia conjunctiva; the large fibre bundles which stain gray are the acoustic lemnisci. Fig. 5 represents a section slightly cephalic to fig. 4. The dorso-lateral bundles of fibres represent the caudal portion of the capsule of the acoustic colliculi, or the acoustic lemnisci just caudad to the colliculi. Mesially are the brachia conjunctiva, while the pontine nuclei and fibres form the ventral portion of the section.

The acoustic colliculi occupy over one-third of the transverse diameter of the brain-stem in fig. 6. They are almost circular and consist of a mass of nerve cells surrounded by a capsule of fibres. The section just



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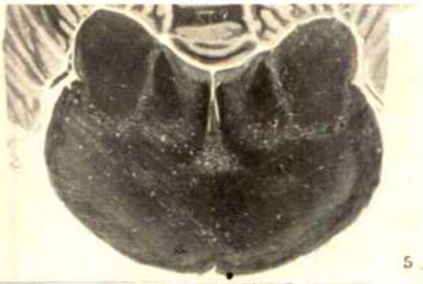

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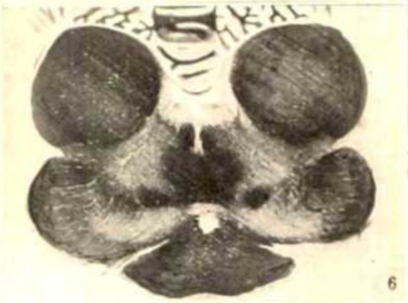

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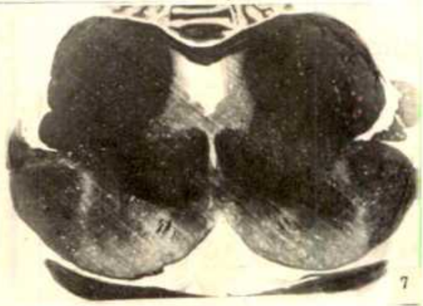

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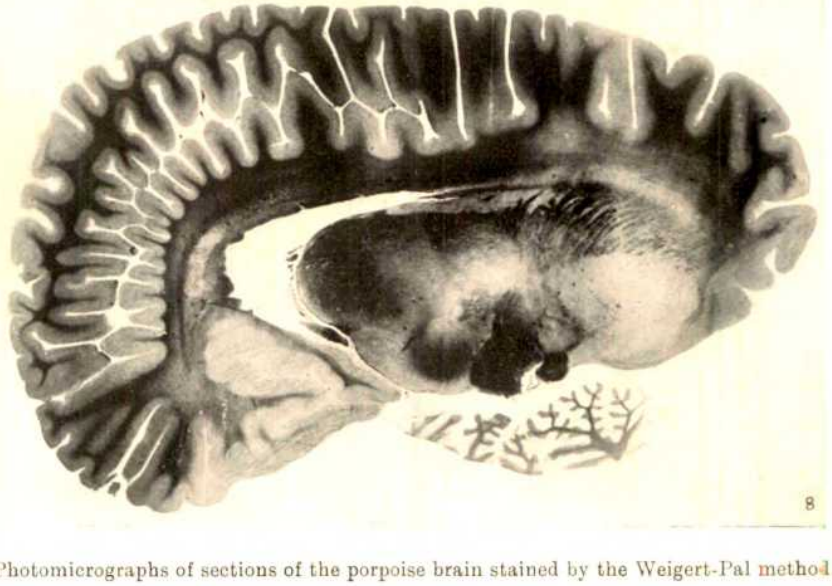

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Photomicrographs of sections of the porpoise brain stained by the Weigert-Pal method.

FIG. 4.—Transverse section of the brain stem. The large grey bundles of fibres at the lateral edges of the section are the acoustic lemnisci.

FIG. 5.—This section cuts the caudal edge of the acoustic colliculi and shows the acoustic lemnisci forming the caudal capsule of the colliculi.

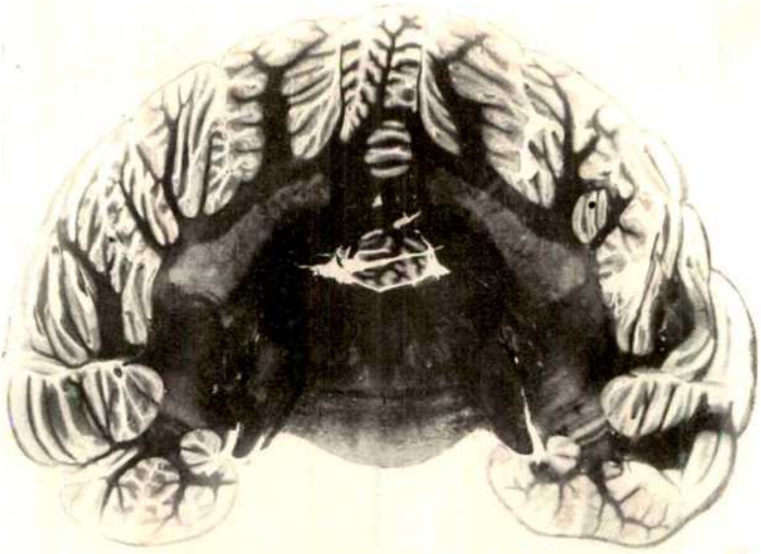
FIG. 6.—Transverse section through the acoustic colliculi.

FIG. 7.—The acoustic colliculi are connected by a group of commissural fibres which lie dorsal to the aqueduct of Sylvius.

FIG. 8.—The caudal prolongation of the thalamus resembles in its contour the optic pulvinar of other mammals. It contains many myelinated fibres. Study of the sections demonstrated that the acoustic fibres end in this region and it is acoustic rather than optic in its connections.

To illustrate paper by Orthello R. Langworthy.

PLATE VI.



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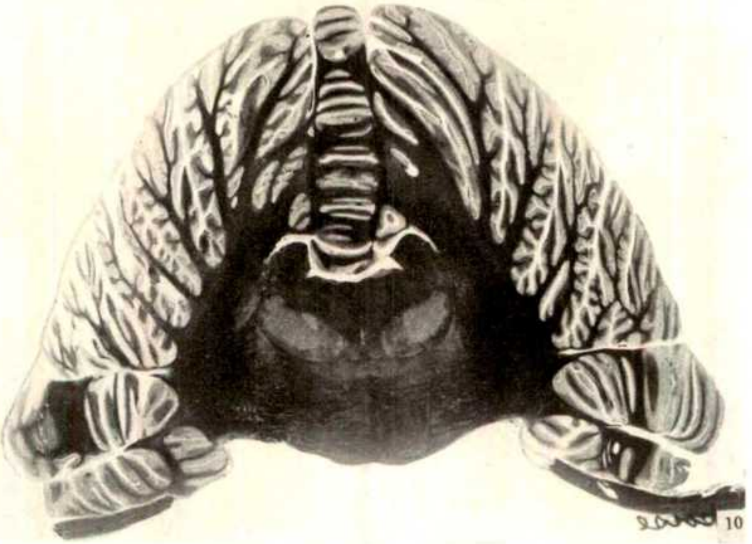

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FIG. 9.—Transverse section through the brain-stem at the level of the acoustic nerves. The cerebellar hemispheres and the flocculi are large; the vermis is compressed in the midline. The dentate nucleus of the cerebellum consists of an almost solid mass of cell.

FIG. 10.—The nuclei of the acoustic lemnisci are large and show as white masses just above the pons. The nucleus of the acoustic lemniscus lies ventro-lateral to the fibres.

To illustrate paper by Orthello R. Langworthy.

cuts the upper end of the pons; the cerebral peduncles project laterally. The pale areas just dorsal to the pons are the substantia nigra; the colour discrepancy is due, of course, to the staining of the section. Fibres of the brachia conjunctiva are crossing in the midline. Ventro-lateral to these fibres are the mesial lemnisci. Dorsal to the brachia conjunctiva the medial longitudinal fasciculi lie close to the midline.

The acoustic colliculi are connected by a group of commissural fibres, shown in fig. 7, above the aqueduct of Sylvius. A portion of the optic chiasma is ventral to the brain-stem. Of particular interest is the separation of the fibres in the cerebral peduncles in a number of tracts.

Fig. 8 is a photomicrograph of a sagittal section through the whole fore-brain, and shows first of all the complexity of the sulci and gyri. The inferior horn of the ventricle can be followed to the tip of the temporal lobe. At the ventral edge of the brain-stem there are three groups of nerve fibres; the one on the right is the optic tract, in the centre the cortico-efferent paths, and on the left acoustic fibres which end in the thalamus.

The corpus striatum may be seen dorsal to the optic tract; in this section the globus pallidus, caudate nucleus and the tail of the caudate nucleus at the dorsal edge of the brain-stem are visible. There is no great development of the putmen in the porpoise.

The caudal prolongation of the thalamus contains numbers of myelinated fibres. It has the contour of the optic pulvinar of mammals, but in reality it is a section of the large acoustic geniculate.

These few photomicrographs demonstrate that the acoustic nuclei and tracts in brain of the porpoise are all large and form the most conspicuous sensory cells and pathways in the brain-stem. The acoustic stimuli must have had the greatest influence on the differentiation of the cortex.

The stimulus of increased numbers of acoustic impulses entering the acoustic colliculi has had no marked effects upon their structure or differentiation. In land mammals the acoustic colliculi have a much more primitive structure than the optic. While the cells of the optic colliculi have a laminated appearance, the acoustic colliculi consist of a solid nucleus of cells surrounded by a capsule of fibres. On macroscopic examination of the acoustic colliculi of the porpoise it seemed possible that the cells might have differentiated into the pattern characteristic of supra-segmental structures in the nervous system. This was not found to be the case and the reason seems quite clear. The optic colliculi differentiated in a laminated pattern in an attempt to form a correlation centre at the time when few sensory fibres other than olfactory entered the pallium. With the development of the neocortex cell all types of sensory impulses are drawn into this region. In other words, there is a strong tendency to the development of dominant centres in the most cephalic portion of the neural tube and in the most cephalic portion of the organism.

The cochlear fibres, therefore, are the conspicuous group of sensory fibres reaching the cerebral cortex. On the basis of these acoustic impulses the temporal lobe has greatly increased in size and has grown posteriorly, carrying the lateral ventricle with it to form the inferior horn of the ventricle. Moreover, large portions of the cortex have been buried to form an island of Reil. Around the acoustic projection centre a wide correlation area has probably developed to synthetize the cochlear stimuli with other types of sensory impulses reaching the cortex.

Many sections of the cerebral cortex were cut and stained with thionin to permit of study of the cyto-architecture. It was hoped that the cortex of the porpoise could be divided into areas, each having peculiarities in the size, shape and arrangement of the cells so that regions could be recognized as clear-cut projection or correlation centres. This is possible in the cortex of Primates, including man. The cells are relatively sparse everywhere in the cortex of the porpoise and they are separated from each other by wide intervals. Moreover the layers of cells are poorly differentiated in most regions. There were a few areas having characteristic structure and these were separated by regions in which the arrangement of the cells was very primitive. In all portions of the cortex the outer, cell-free layer is wide. A definite layer of granular cells may be demonstrated in all parts except in the motor area. The infra-granular pyramidal cells show no remarkable development and the supra-granular pyramidal layer is everywhere thin. Certain areas, however, may be identified. The motor cortex lies at the very frontal pole of the cortex ; the visual projection area surrounds the calcarine fissure on the mesial tip of the occipital lobe. The acoustic fibres enter the temporal lobe just posterior to the Sylvian fissure. The region that gives rise to the temporo-pontine tract has also been identified. The fibres of cutaneous and deep sensation enter the cortex just posterior to the motor area. A great deal of the remaining cortex has a very primitive cytological pattern and this must be considered as rather undifferentiated correlation cortex.

With the rapid development of the cerebral cortex concurrent with the acquisition of binocular stereoscopic vision in Primates, the motor cortex underwent great differentiation, particularly in reference to the innervation of the fore-leg. The fore-leg lost its locomotor and postural functions and became useful for climbing trees or carrying food to the mouth. No motor development along these lines was required in the porpoise where the hind-leg is not developed on the surface of the body and the fore-leg has differentiated into a short flapper.

Microscopic study of the cerebral cortex of the porpoise demonstrated a motor area near the frontal pole of the brain. Anterior to this one was the modified motor area, or area frontalis, which gives rise to the fronto-pontine tract. Both these areas are rather large and the area frontalis extends on to the ventral surface of the frontal lobe so that there is no frontal correlation area in the porpoise similar to that present in Primates. The cortico-spinal and fronto-pontine tracts may be followed into the cerebral peduncle as well-defined bundles. The largest efferent bundle in the cerebral peduncles is the temporo-pontine tract, which contains large numbers of fibres.

The cerebellum is of great size in the porpoise and the hemispheres, in particular, are very well developed. It is known that the cerebellar hemispheres differentiate coincidently with the cerebral hemispheres. Both are large in the porpoise and it would be expected that there would be marked connecting tracts between them. This is indeed the case as evidenced by the large sized pons. The efferent fibres from the cerebrum do not run through the pons but dorsal to it, and the fibres turn ventrally to end around the pontine cells. On the efferent side of the cerebellar reflex arc, many fibres of the brachium conjunctivum end in the thalamus and undoubtedly are relayed back to the cortex.

In connection with the cerebellum of the porpoise it is interesting to recall the theory of certain comparative anatomists that the vermis controls the trunk musculature, the hemispheres the limb musculature of the body. The porpoise has no hind-legs and the fore-legs have developed into flappers. Yet the hemispheres of cerebellum are very large.

Finally, a word concerning the efferent paths from the brain influencing the anterior horn cells of the cord. These require further study. The cortico-spinal fibres cannot be traced in sections stained by the Weigert-Pal method below the lower end of the medulla. Either they are relayed at this level or travel caudad as non-medullated fibres. The red nucleus is rather small in the porpoise, as is also the rubrospinal tract. The vestibulo-spinal and tecto-spinal tracts are also small.

In summary, the cochlear division of the acoustic nerve shows great development in the porpoise and the acoustic nuclei and tracts in the brain-stem are very large. Large numbers of fibres carry acoustic impulses to the cortex and it is probable that these impulses have played a great part in the differentiation of the cortex of the porpoise.

Coincident with the growth of the cerebral cortex the cerebellum has become large; the hemispheres and flocculi show particular development. The connections between the cerebral and cerebellar hemispheres are well differentiated and large cortico-efferent pathways connect with the pontine cells. The porpoise is a powerful and graceful swimmer, and these pathways probably carry impulses that produce a precise control of the tone and contraction of the striated muscles of the body.

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NOTICES OF RECENT PUBLICATIONS.

The Selected Writings of John Hughlings Jackson. Vol. 1. "On Epilepsy and Epileptiform Convulsions." Edited by JAMES TAYLOR, with the assistance of GORDON HOLMES and F. M. R. WALSHE. London: Hodder and Stoughton. 1931. Pp. 500. Price 25s.

The increasing influence upon modern neurological thought of the ideas of Hughlings Jackson is a welcome sign that can have escaped no student of the neurological literature of this country. Of equally favourable augury for the future of neurology is the evidence that continental neurologists also are coming to appreciate the significance of Jackson's work. Thus, some years ago Arnold Pick dedicated his great contribution to the study of speech disturbances to Jackson as "the deepest thinker in neuropathology of the past century," while more recently translations of certain of his lectures have appeared in German.

All this is the more remarkable tribute to the genius of Jackson when we consider that to the present generation much of his work is a closed book. Not until 1925 was there even an available bibliography of his writings, which were to be found only by arduous search on the shelves of great medical libraries and in the columns of hospital reports and medical periodicals, many of them long since extinct. In 1925, Dr. James Taylor, the editor of the present selection of Jackson's writings, collected and re-published his shorter notes, known as "Neurological Fragments," and appended thereto a complete bibliography of his published works. In preparing the two volumes, of which the present is the first, Dr. Taylor has completed his pious task, and in doing so has earned the warm gratitude of all neurologists.

In virtue of their being so inaccessible, and because also of the abstract quality of much of Jackson's thought, his views have not infrequently been incompletely understood and ineptly cited. In this selection of his writings their author speaks for himself, and it would be unfitting, as indeed it would be impossible, to attempt within the compass of this brief notice any summary of Jackson's contribution to medicine. It may not be inexpedient, however, to consider briefly some of the lessons we may derive from his work. They are lessons of scrupulously careful clinical observation, of what Trotter has aptly described as an "unresting contemplation" of the facts of observation, and of an unparalleled degree of scientific insight.

The seas Jackson so skilfully and so triumphantly sailed were uncharted to an extent it is difficult for us of this generation to realize, yet unless we do realize this we may fail to see the magnitude of his achievement. If we are to understand the depth and the philosophic quality of his thought we must try to recall the state of knowledge concerning the physiology of the nervous system some sixty years ago. That Jackson's views, so largely speculative when he formulated them, should have received so striking a measure of confirmation, not alone from the labours of succeeding generations of clinical observers, but also at the hands of such a master of the experimental method as Sherrington, shows upon how sound a foundation of clinical observation and clear thinking they were built. Thus, not the least of the lessons we may learn, and it is one by which each of us may profit, is the primary duty of precise and adequate clinical observation. In the logical sequence and development of his thought throughout the series of papers on convulsions, we see a rational and masterly progress from observation to generalization.

To the mind of the neurologist there will occur a small and select number of the writings of bygone masters in this branch of medicine, to which he unfailingly returns from time to time, either for the treasures of clinical wisdom and knowledge they contain, or for a stimulus and inspiration in his own work. It is in the latter class that Jackson's writings will come to occupy a unique position.

Much praise is due to Dr. Taylor for his enlightening introduction to this volume, and for the care he has taken in collecting and editing the papers it contains, and in verifying the numerous cross-references which it has been necessary to insert. Neurologists will look forward to the appearance in the coming autumn of the second volume which will contain all Jackson's publications on other neurological subjects which it is thought profitable to reprint.

The Diagnosis and Treatment of Brain Tumours. By ERNEST SACHS. London: Henry Kimpton. 1931. Pp. 396 with 224 illustrations. Price 42s.

The increasing interest in tumours of the brain, and particularly the development of neurological surgery, has led to the appearance of numerous textbooks and monographs on this subject during the past few years, and the volume under review will take an important place among them. The author is a well-known neurological surgeon who rightly insists on the necessity of a thorough training in neurology for anyone who aspires to undertake the operative treatment of intracranial growths, and his book is consequently written largely from the clinical point of view. Yet this is its most disappointing feature; the groups of symptoms which characterize lesions of different parts of the brain are recorded, often in tabular form, and some of them are discussed, but their significance and their value in localization could have been dealt with more simply and in a manner more useful to the surgeon who seeks assistance from the author's experience. The disturbances of speech, for instance, are presented mainly as extracts, occupying a few pages, from Head's monograph on aphasia, which, admirable though it is, will be of little use to the student confronted with the problem of determining the site of a lesion producing any type of aphasia. The chapter on convulsions is particularly incomplete, many of the distinguishing features of those due to local disturbances in different regions of the brain being neglected or mentioned without due emphasis on their importance in the problem of localization. The discussion of tumours of the cerebellum also lacks that intimate relation to the symptoms seen at the bedside which can enlighten the student or surgeon as to the exact significance of his clinical observations, and unfortunately the citation of cases, typical though they may be, cannot replace this. Several obvious mistakes have crept into the clinical sections, as the explanation of a typical grasp reflex by paralysis of the extensors of the fingers.

These defects only illustrate the great difficulty in the adequate treatment of the task which the author has undertaken, for the localization of cerebral tumours by clinical methods requires all the knowledge and experience that has been acquired by neurologists within the past fifty years, and to present these properly, even in summary, and with a critical regard to their significance, is evidently impossible in a book devoted mainly to surgery. Ventriculography and other methods employed in localization are carefully described and their value indicated. The chapter on surgical pathology is excellent, though it contains little that is new. That on operative technique and post-operative treatment also represents admirably the author's methods.

Les Tumeurs cérébrales; leurs Manifestations et leur Traitement chirurgical. Par Th. de MARTEL et J. GUILLAUME. Paris: G. Doin et Cie. 1931. P. 136. Price 70 francs.

All the cases of intracranial tumour treated by operation in the Neuro-Surgical Institute of Paris, 35 in number, between December, 1929, and April, 1930, are described by the authors in this volume with few comments or remarks on the problems presented by the individual patients. Their acknowledged aim has been to present to their colleagues who have little experience of neurology the possibilities of cerebral surgery. The descriptions of the clinical symptoms and of the operative technique are meagre, but the volume contains some interesting observations. Their enthusiasm will probably be tempered by further experience; one of their main conclusions is that when an intracranial tumour is suspected further investigations may be prejudicial to the patient, even exact localization being unimportant as the line of approach is identical in all cases.

La Sciatique. Par J. A. CHAVANY. Paris: G. Doin et Cie. 1931. P. 51. Price 18 francs.

Though this small volume is devoted chiefly to its treatment, a very thorough description of the clinical features of sciatica is given and its differential diagnosis fully discussed. The clinical side of the subject is dealt with under the headings, simple or primary sciatica, which, as Sicard, he regards as due to a massive affection of a rheumatic nature of the structures through which the nerve passes in the sacrum, pelvis and hip; symptomatic sciatica, in which the pain is only a manifestation of some other disease, and pseudo-sciatica.

The section on treatment contains a comprehensive review of the therapeutic measures that have been used with success, much attention is being given to local and paravertebral injections.

Les Syndromes cérébelleux mixtes. Par A. de ALMEIDA PRADO. Paris : Masson et Cie. 1931. P. 168. Price 30 francs.

This volume by a recently deceased Brazilian neurologist has been admirably translated into French by Dr. Nathan. It is based entirely on French work, and includes those clinical conditions not due to the primary disease of the cerebellum, in which, however, symptoms of disturbance of cerebellar functions are a prominent feature. The so-called syndromes of the superior, middle and inferior peduncles of the cerebellum, those due to the compression of the cerebellum, and those which appear occasionally in other diseases, as general paralysis, encephalitis lethargica and disseminated sclerosis, are described in separate chapters. The author's personal experience has evidently been small, in fact his book consists almost entirely of extracts of French literature made with little evidence of critical discrimination. The subject is presented as a series of "syndromes," many of which are based on a single clinical observation and recorded without regard to their physiological significance and often, too, of their anatomical substratum. The uncritical inclusion of all published cases relevant to his subject and the neglect of most of the recent work which has not appeared in French literature naturally robs the book of much of the value it might have had, but it contains a number of extracts of observations that may be useful to neurologists interested in the symptomatology of lesions of the brain-stem.

Die beginnende Paralyse : eine klinische und psychopathologische Studie. Von H. BÜRGER PRINZ. Berlin: J. Springer. 1931. S. 86. Price RM. 7.80.

The important question whether the clinical form of early dementia paralytica has any prognostic importance for treatment by malaria is one of the main subjects of this monograph, but it contains an interesting analysis of the various types of the early disease, before and after treatment, and especially of their psychological aspects. From his investigation of fifty-six cases, the author believes that the prognosis is bad in depressive and hypomaniacal cases, and in those with evidences of general dementia and pronounced symptoms of organic disturbance. A chapter on the nature of the dementia and the factors that influence or contribute to it is an excellent essay to a matter of great interest.

The Inborn Factors in Disease: an Essay. By ARCHIBALD E. GARROD. Oxford University Press. 1931. Pp. 160. Price 7s. 6d.

This little book on predisposition to disease makes no attempt at being an exhaustive treatise on the subject. After a historical survey of the various interpretations or uses of the word "diathesis", it is divided into two parts, the first on the basic principles of predisposition and the second on the several kinds of predisposition. A very suggestive chapter is that on the chemical basis of individuality; and in that on "the inborn factors in infective diseases" the physician whose conception of a disease is dominated by its ætiology will find much food for thought. The author's bias towards biochemistry is everywhere apparent, but errors of metabolism form a small part only of the subject matter. It is disappointing that the word "abiotrophy" is still used without any attempt at explaining it in terms of metabolism; the author merely suggests the possibility that the tissues "may be damaged or rendered sensitive to damage, by the presence in them of some metabolic product which progressively impairs their integrity." Obviously it is too early yet for us to envisage life altogether in terms of chemistry, but the author sees in biochemistry the best approach to the study of mutations and hereditary predispositions.

The Science of Psychology. Introductory Study. By RAYMOND H. WHEELER. London: Jarrolds, Ltd. 1931. Pp. 556. Price 21s.

Professor Raymond Wheeler has written a textbook which should prove of great value to students who have already acquired a basic knowledge of modern psychology. The excellence of the book lies not so much in the broad field which has been covered with a considerable degree of detail, as in the fairness with which the various schools of thought are discussed, and the clarity of the exposition. The exposition is in a way unique in that it starts off with a lengthy chapter on social behaviour before passing on to deal with the manifestations of individual psychology. Emotive behaviour and intellectual behaviour are fully dealt with under various heads, and wherever the subject needs further elucidation the student is liberally supplied with references. The important subject of learning is discussed, with its experimental methods in two long chapters. The latter part of the book deals with what he calls observational behaviour, that is to say, with the characteristics of sensory experience and perception. The book ends with an up-to-date treatment of the nervous system and its relation to behaviour.

This order of exposition is particularly attractive in that it leaves the Behaviouristic approach to human behaviour to the end after the student has acquired a knowledge of psychological processes as seen by observation and introspection. In other words, the theory of Behaviourism, as expressed in neurology, is brought out without giving the reader an initial bias. Each chapter has an excellent bibliography.

Die Denkmethoden und ihre Gefahren. By VERA STRASSER. Leipzig: Georg Thieme. Pp. 526. Price 20 marks.

This large volume deals with the complexity of human psychological reactions in their various departments of human life. The burden of the book is to bring into relief the methods of investigating psychological disturbances and the dangers inherent in such methods. In carrying out this stupendous task, the author has plumbed the depths of philosophical analysis, not only of the methods, but of the concepts used in psychological discussion. The book can be recommended only to those psychopathologists who have philosophic training and plenty of time.

Conditions and Consequences of Human Variability. By RAYMOND DODGE. New Haven: Yale University Press. Pp. 162. Price $2.50

Although Professor Dodge attacks the problem of human behaviour and its variability in a distinctly philosophic manner, he is in constant contact throughout this book with the modern problems of functional neurology. He is conscious, as many are, of the methodological difficulties underlying both neurology and psychology, and his restatement in this monograph of our present-day knowledge of the integrative action of the nervous system, and its relation to psychology, is very welcome. He deals at the outset with the general problem of variability with reference to sensibility and the conditioning of responses. He then passes on to a consideration of relative fatigue, and the refractory phase. Inhibition and summation are subtly discussed in the light of the latest work of Lucas, Adrian, Forbes, and Pavlov. The effect of faint stimuli has a chapter to itself, and its psychological implications are touched upon. In dealing with cortical function, in particular, his consideration of the interaction of neural strata and of cortical systematization is particularly suggestive to all those who wish for a closer liaison between neurology and psychology. The book closes with a philosophical discussion of the relationship of mind and brain. This is a book that can be highly recommended to all those who regard neurology as something more than the study of organized grey matter. It can be called the study of dynamic neurology.

Handbuch der Geisteskrankheiten. Herausgegeben VON OSWALD BUMKE. 5ter Band. Spez. Teil 1. Seiten 578 mit 10 Abbildungen. Berlin: J. Springer. 1928.

Handbuch der Geisteskrankheiten. Herausgegeben VON OSWALD BUMKE. 10ter Band. Spez. Tiel 6. Seiten 374 mit 64 Abbildungen. Berlin: J. Springer. 1928. Price RM. 36.00.

Like the other parts of this System of Psychiatry, the present volumes are critical and thorough, inclining to conservatism wherever speculation seems to have outrun the data of immediate observation. In Volume V the psychopathic reactions and dispositions are presented in great detail, with an introductory account by Birnbaum of the modern views on the structure of psychosis. A short section by Stertz on the neurasthenic reaction is followed by J H. Schultz's attempt, on the whole a successful one, to describe the ill-defined condition "constitutional nervousness": for him it is a diagnosis made by elimination, though with genetic and constitutional implications. The succeeding two sections cover the whole range of neurosis and psychopathic disposition; the customary divisions into hysteria, compulsion neurosis, anxiety forms, etc., are sacrificed for a less formal mode of presentation, with the emphasis on proneness to react along comprehensible lines according to constitution and previous experience. None of the rigid formulations, however assertive, complex or "dynamic," are accepted as adequate and final in the general section by E. Braun on "Psychogenic Reactions," while Eugen Kahn's exhaustive monograph on "Psychopathic Personalities" is of remarkable breadth and restraint.

The concluding section on Psychotherapy has been written by J. H. Schultz, who shows that successful treatment of these disorders is not by any means the prerogative of well-meaning enthusiasts or jargon-equipped muddlers, and that treatment may be not only successful but even intelligent without being limited by the tenets of one school.

The first half of Volume X deals with congenital mental defect, and defect acquired in early childhood. The section on the psychotic complications is rather short for so comprehensive a study; and in the unduly concise description of intelligence tests there is, as elsewhere, scant regard for non-German work. The author's criticism of the mental-age method of assessing defect is, however, trenchant and deserves emphasis. Mental disorders associated with thyroid deficiency are described at rather disproportionate length by Gamper and Scharfetter; congenital and infantile myoxœdema and endemic cretinism are of only limited interest outside the areas where they are common. The work has been carefully done and will be of interest to the specialist in thyroid disorders.

Psychotherapie bei organischen Erkrankungen. By FRITZ MOHR. Leipzig: Georg Thieme. 1930. Pp. 103. Price 3 marks.

This is a slender and attractive volume on a topic which has only too belatedly come to the front. It deals with the treatment of the psychological accompaniments of physical diseases, and in addition, although in a less degree, with the occasional psychological causes which may precipitate organic disease. It opens with a discussion of general psychopathological considerations and then passes on to the physical and mental methods of dealing with organic diseases. Hypnosis, psycho-analysis, waking suggestion, and re-education are fully discussed. The final chapter deals with particular disorders and actual examples of cases.

Brain and Personality. By PAUL SCHILDER, M.D., Ph.D. Nervous and Mental Disease Publishing Company: New York and Washington. 1931. Pp. 136. Price $3.00.

The first part of this book deals with the psychological aspect of cerebral neuropathology; it is a summary of the author's views on the relationship between psychic and organic, as presented in numerous earlier publications, and contains chapters on speech disturbance, optic agnosia, tone and posture, and consciousness. They are in the main loosely connected studies, with evidence of wide reading and bold, if stimulating, thought.

The other part, on the relation between the personality and the motility of schizophrenics, is built around clinical observations, reported in some detail. The chief objection to Schilder's method is that he correlates phenomena which may be of different nature, and from this correlation infers a similarity in the functional change and morphological substrate. His chief effort is to bring about a synthesis, or to find a common explanation for "the problems of the motility and the problems of the emotions of the schizophrenic," but there is a more or less tacit assumption that the latter are the prime movers.

L'Hallucination. Par PIERRE QUERCY. Philosophes et Mystiques, pp. 381. Etudes cliniques, pp. 560. Paris: Felix Alcan. 1930.

This large work is a semi-philosophical treatise dealing not merely with hallucinations in the strict sense but with the whole problem of sensation and perception. The first volume is concerned mainly with the systems of three philosophers, Spinoza, Leibnitz and Bergson, and the experience of one mystic, the famous Saint Theresa de Ahumada. After discussing the arid speculations of the philosophers, Quercy turns to the autobiography of that remarkable woman, lately the subject of renewed interest in France. He examines her visions and those of St. John of the Cross, from the point of view of the theologian as well as of the philosopher and the clinician, and adduces the relevant doctrine of the mediæval schoolman, Gerson.

The second volume, of clinical studies, covers a wide field: coloured vision, hypnagogic hallucinations, dreams, the phenomena of mescalin and other intoxications, and illusions of many kinds are among the objects of the author's restricted method of investigation. The work of E. R. Jaensch, on eidetic imagery, has a valuable, rather sceptical chapter to itself.

These subtle and skilfully written volumes represent a method of approach which is not that of the psychiatrist or the neurologist, but is none the less sound and, from the point of view of epistemology, essential.

Das Stehen. Statische Reaktionen, Gleichgewichtsreaktionen und Muskeltonus unter besonderer Berücksichtigung ihres Verhaltens bei kleinhirnlosen Tieren. Von. G. G. J. RADEMAKER. S. 476 mit 296 Textfiguren. Berlin: J. Springer. 1931. Price Rm. 69.60.

Recently the editors of the *Journal of Pathology* have sought to impress upon their contributors the duty of brevity, by printing in a number of the Journal the following anonymous aphorism:—

> "Buddha wrote nothing, Christ but once, in the dust.
> The 'Agricola' of Tacitus contains only 7,000 words,
> and the whole of Thucydides would go into a large
> issue of the *Times*."

Even the most determined reader, faced by this mighty monograph of some 200,000 words, must wonder whether what its writer has to contribute to knowledge might not have been more concisely conveyed.

In the student of so complex and highly technical a subject as that dealt with by Professor Rademaker, it is surely reasonable to assume a working acquaintance with the relevant literature and a thorough knowledge of those pioneer investigations of Sherrington and Magnus out of which it has arisen. Yet in page after oppressive page of small, close-knit type we are given all that has been written, profitably and otherwise, by experimentalists and clinicians upon every aspect of the subject. With a literature that grows almost faster than any interested student can master it, ultimately it will ensue that if every writer is to cumber his own fresh additions to knowledge with an up-to-date history of his subject, papers and monographs will soon reach dimensions that will defy the printer and eliminate all readers.

Further, in his original papers and in the monograph that so admirably crowned his investigations, Professor Magnus conceded to his readers the inestimable boon of a concise summary of its principal contents at the end of each chapter. Not the least of the obstacles that Professor Rademaker places between his readers and himself is the withdrawal of this aid to easy and comfortable study.

Nevertheless, those who are sufficiently keen to follow the author will find an important contribution to the physiology of posture, and a careful analysis of the symptomatology of cerebellar extirpation in animals.

In briefest summary, Rademaker finds that after extirpation of the cerebellum, all those postural and stato-kinetic reactions that underlie the maintenance and harmonious variation of posture in the intact animal persist. There is no loss of these reactions, but a "release" of activity in which the reactions take on features of excess and of impaired maintenance and adjustment. He rejects as elementary components of the syndrome of cerebellar defect, the astasia, atonia and asthenia of Luciani, regarding these phenomena when they are seen at all as transient, and of the order of "shock" symptoms.

But while such a minute analysis of cerebellar ataxy as he has achieved is an essential preliminary to any conclusive and detailed theory of cerebellar function, it does not appear that such a theory is yet within reach. Rademaker contents himself with the general statement that the cerebellum exerts a regulating influence not only upon those co-ordinated muscular reactions that are subserved by the brain-stem and cord and arise in exteroceptive and proprioceptive stimuli, but also upon reactions arising in the distance receptors and traversing the cerebral cortex. He rejects the hypothesis that the cerebellum is no more than an instrument by which the cerebral cortex analyses and synthesizes the reflex reactions mediated through the brain-stem and cord, in the production of normal voluntary movement.

The observation of Magnus and others that the well co-ordinated and highly complex motor reactions of the thalamus animal are not disordered by subsequent decerebellation have made it seem probable that the cerebellum does not function in the absence of the fore-brain and thus does not participate in the fundamental processes of co-ordination of movement. Rademaker has made but a single experiment to test this hypothesis, and on the basis of this observation he rejects it. The experiment consisted in extirpating the cerebellum in a dog from which the fore-brain had already been removed some weeks earlier. This dog after the cerebral extirpation presented the well-known activities of a dog without a fore-brain, but after the subsequent decerebellation its movements presented all the essential features of cerebellar deprivation in an otherwise intact animal. The animal succumbed to infection some five weeks after the last-named operation. We are not justified, therefore, in accepting as final the result of an isolated and prematurely terminated observation. But if it be confirmed by further and more conclusive experiments, its bearing upon our conception of cerebellar function will be of the first importance.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

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EDITOR.

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BRAIN.

PART 3, VOL. 54.

THE EXPERIMENTAL PRODUCTION AND PREVENTION OF DEGENERATION IN THE SPINAL CORD.

BY EDWARD MELLANBY.

(Department of Pharmacology, University of Sheffield.)

IN 1926, E. Mellanby described before the Physiological Society experimental work in which degenerative changes of nerves in the spinal cord of dogs were produced and prevented under certain dietetic conditions [1]. Since then developments of this work, especially in relation to ergot, have been from time to time described in lectures before medical and scientific bodies [2 and 3].[1] The investigations have made but slow progress and even now the subject is in an elementary stage. The experimental procedure as at present used is prolonged and the unravelling of the factors involved has necessitated the examination and the elimination of many food elements. A sufficient number of facts have, however, come to light to warrant their description, and it is hoped that this publication will hasten the further elucidation of a physiological and pathological problem which may have a wide bearing on nervous disease in man. Some of the experimental symptoms and lesions produced in the dogs, and the manner in which these are produced and prevented, are so reminiscent of nervous ergotism, pellagra and lathyrism, found in man, especially in times of dietetic restriction, that the experiments seem certain to throw light on the ætiology of these human illnesses. Their significance may, however, be of wider interest, for demyelination of central nervous system fibres is a characteristic change, although it is found in such varied diseases as pernicious anæmia, tabes dorsalis, disseminated sclerosis, general paralysis, post-vaccinal encephalitis and cancer. The experimental work may also have some bearing on the causation and control of these conditions. A discussion on its possible significance will be given at the end of the report.

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[1] In addition to the occasions referred to, the facts mentioned below, except those concerning the action of carotene, were described before the Manchester Medical Society, October, 1928, and also in a series of lectures given at University College, London, in May, 1929.

Since Eijkman's classical work published in 1897 [4] in which he produced polyneuritis gallinarum by means of diet, it has been recognized that the structure and function of peripheral nerves are controlled by a specific dietetic ingredient, namely vitamin B_1. Eijkman's discovery formed the starting point of that fruitful field of study which embraces the group of pathological conditions known as "deficiency diseases," a group which includes scurvy, rickets, infantile tetany, dental hypoplasia and caries, periodontal disease (pyorrhœa alveolaris), pellagra and probably certain types of bacterial and worm infection. Of course there are, in some of these at least, other factors at work than the specific deficiency, but generally speaking, the other factors are harmless provided there is or has been no specific dietetic deficiency. Evidence will be given in this paper to show that demyelination of spinal cord fibres is yet another instance which illustrates, among other things, the importance of specific dietetic factors in physiological development and function.

Apart from the work of Orr and Rows [5] who studied spinal cord degeneration produced by bacteria and bacterial toxins, experimental investigation on this aspect of the central nervous system has not been very fruitful. In 1916, Hart, Miller and McCollum [6] described changes in the anterior horn cells of pigs' cords produced by means of dieting. The changes described by these authors included shrinkage of the motor cells especially those of the ventro-medial and ventro-lateral columns, crowding of Nissl's granules, the near obliteration of nucleus and nucleolus, and degeneration of the processes. No changes in the conducting fibres of the spinal cord were described. The authors decided they were dealing with a form of beri-beri, not, however, due to a deficiency of vitamin B, which was present in abundance in the wheat germ portion of the diet. Indeed the pathological condition was ascribed to a toxic action of the wheat germ. By supplementing the diet with alfalfa meal and meat scraps the cell changes were prevented. They ascribed the protective effects of these foodstuffs to a combined action of additional proteins, fat-soluble vitamin and a better salt mixture, but did not consider that any one of these substances could in itself afford protection. As far as I know, they did not follow up this work.

More recently an account of an investigation bearing closely on the present work has been published by Hughes, Lienhardt and Aubel [7], in which is described the experimental production of degenerated fibres in the spinal cord and peripheral nerves of animals by means of diet. Young pigs were fed from the time of weaning on white corn, tankage and bone ash and in six to ten months developed blindness, inco-ordination and spasms. On post-mortem examination degenerative changes were found by these workers in the spinal cord and in the optic, sciatic and femoral nerves. The addition of cod-liver oil, butter fat, yellow corn and alfalfa leaf meal prevented or relieved the condition, and thus the preventive factor was probably vitamin A.

Finally, there remain for reference some interesting results obtained by Castle. For an account of this work I am indebted to Dr. Castle and for the privilege of seeing his unpublished manuscript. He fed a number of dogs on diets deficient respectively in vitamins B_1 (anti-neuritic) and B_2 (pellagra-preventing), and some with a combined deficiency of both vitamins. In all the animals deprived of the anti-neuritic vitamin he found post mortem a diffuse, irregular loss of myelin chiefly in the white matter of the cord and some in the cerebral cortex. In nine out of these fourteen animals slight lesions of the peripheral nerves were also found. Early changes were found post mortem in the nervous system of four dogs fed on the diet deficient in vitamin B_2, but in life the animals did not show any significant neurological symptoms. It is of interest to note that the nervous symptoms in the animals deprived of vitamin B_1 could always be improved within a few hours by the administration of a source rich in this substance. This particular observation of Castle's is reminiscent of the rapid results seen in avian beri-beri following the administration of vitamin B_1 and suggests that the problem here is a similar one to that of avian beri-beri rather than to that of combined system disease seen in human beings.

The history of the present investigation dates back to the time when experiments were made on puppies with the object of determining the ætiology of rickets (E. Mellanby) [8]. The rachitic animals often developed great weakness, especially noticeable in the hind legs; the weakness was sometimes associated with spasticity. At first it was thought that the muscular weakness was one of the manifestations of rickets and this idea was supported by the fact that substances, such as cod-liver oil and milk, which cured or prevented rickets cured or prevented the muscular weakness. At a later stage in the work (1923) it was noticed that some of the experimental animals developed severe inco-ordination when they attempted to walk, and it was this inco-ordinated gait which led to the examination of the spinal cord by histological methods. It was soon realized that there was more in the problem than rickets, for although some rachitic animals showed degenerative changes in the spinal cord, others did not. Indeed, there was no definite relationship between the pathological changes in the bones and the nervous system. Throughout much of the original work on rickets, which led to the establishment of the anti-rachitic vitamin, there was no clear differentiation between the anti-rachitic vitamin (vitamin D) and vitamin A, and this fact, as will be seen later, resulted in confusion of the explanation of the nerve degeneration results. Indeed, it was only possible in this case, as in the problem of susceptibility to bacterial infection and its relation to diet, to begin to sort out the various experimental phenomena observed when the differentiation between vitamins A and D was finally established.

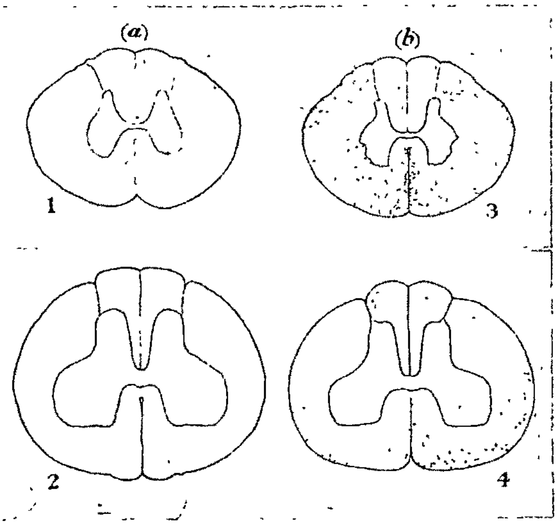

FIG. 1.—Drawings representing the distribution of degenerating nerve fibres as shown by the Marchi technique in the spinal cords of (*a*) and (*b*). (Experiment I.) Drawings 1 and 2 represent sections through the 2nd cervical and 6th cervical regions respectively of (*a*) (white flour). Drawings 3 and 4 are corresponding sections of (*b*) (white flour plus wheat germ). Note the greater amount of degeneration in the cord of (*b*), and also that the degenerating fibres are more scattered in the higher region.

Although it soon became obvious that a fat-soluble vitamin played a part in preventing the cord degeneration, attention was first focused on the positive aspect of the phenomenon, for it seemed probable that just as cereals had an interfering action on bone calcification [9] so also they would under certain conditions exert a toxic effect on the nervous system. Difficulties were, however, encountered in the variable results obtained in different litters of puppies. In some litters the spinal cord degeneration could be easily produced when the diet contained much cereal and was deficient in fat-soluble vitamins. On the other hand, some litters were refractory and showed no cord changes during the experimental period. In those litters giving a positive result, although the addition of wheat germ usually made the cord changes more extensive, yet those eating white flour alone as the cereal part of the diet sometimes developed fairly marked degenerative changes in the spinal cord.

Some of these discrepancies are now easier to understand in the light of further experimental work.

It may be well before describing later developments to illustrate some of the positive results obtained with diets containing white flour, oatmeal and wheat embryo as cereals because it is important that it should be recognized that the pathological changes can often be produced by natural foodstuffs.

EXPERIMENT I.

Production of Spinal Cord Degeneration by Diets which include White Flour and Wheat Germ.

Age beginning: 10 weeks.

Duration of experiment: About 4 months.

Basal diet: Separated milk powder, 20-30 grm.; lean meat, 20-10 grm.; peanut oil, 10 c.c.; dried yeast, 2·5-5·0 grm , orange juice, 3-6 c.c.; sodium chloride, 1-2 grm.

(*a*) had white flour.

(*b*) had 60 per cent. white flour, 40 per cent. wheat germ.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(*a*)	—	Little degeneration	Active during much of experiment. Fairly steady on legs but weak
(*b*)	Wheat germ	Much degeneration	Very inco-ordinate. Puts legs down slowly and unsteadily later paralysed

The rate of growth of the two animals was similar.

The degenerative changes of the cords of these animals when stained by Marchi's method are represented in fig. 1.

In this experiment, degeneration developed in the spinal cords of both animals, but in (*b*), with wheat germ added to the diet, it is more extensive.

Another experiment giving similar results may be quoted.

EXPERIMENT II.

Production of Spinal Cord Degeneration by Diets which include Oatmeal and Wheat. Germ.

Age beginning: 7 weeks.
Duration of experiment: About 3 months.
Basal diet: Separated milk powder, 20 grm.; lean meat, 20-10 grm.; peanut oil, 10 c.c.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; salt, 3 grm.
(*a*) had oatmeal.
(*b*) had 80 per cent. oatmeal, 20 per cent. wheat germ.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(*a*)	—	Little degeneration	Nearly normal .. .. ..
(*b*)	Wheat germ	Fair amount of degeneration especially in Cii, in anterior, antero-lateral, and direct cerebellar tracts	Hind legs stiff; later dragged hind legs when walking; later still inco-ordinate

The rate of growth of the two animals was good and comparable during the greater part of the experiment, but towards the end both lost weight, especially (*b*).

These two experiments illustrate the fact that degenerative changes in the cord can be produced in young dogs by diets rich in cereals when the fat-soluble vitamin intake is deficient.

In the following experiments it is demonstrated that the degenerative changes can be prevented by adding to the food a source of fat-soluble vitamins. In the first of these experiments olive oil and butter are compared; in the second, butter fat is used with its fat-soluble vitamin content respectively intact and destroyed by heat and oxidation.

EXPERIMENT III.

Production of Spinal Cord Degeneration by Diets which include Bread, Wheat Germ and Varying Quantities of Fat-soluble Vitamins.

Age beginning: 7 weeks.
Duration of experiment: About 2 months.
Basal diet. Bread (80 per cent.) and wheat germ (20 per cent.); separated milk powder, 20-25 grm.; lean meat, 10-20 grm., yeast, 3-5 grm.; orange juice, 3 c.c.; salt, 1 grm.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(*a*)	Olive oil, 10 c.c.	Much degeneration	Could not walk straight; had fits occasionally. Inco-ordinate, and finally paralysed. Eyes ulcerated
(*b*)	Butter, 10 grm.	No degeneration	Normal

Both animals grew well for the greater part of the experiment.

EXPERIMENT IV.

Production of Spinal Cord Degeneration by Diets which include Bread, Wheat Germ, Treated and Untreated Butter Fat.

Age beginning: 8 weeks.

Duration of experiment: About 4 months.

Basal diet: Bread (80 per cent.) and wheat germ (20 per cent.); separated milk powder, 20 grm.; lean meat, 20-10 grm.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; salt 1 grm.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(*a*)	Olive oil ..	Much degeneration	Looked dazed; abnormal gait; later paralysed
(*b*)	Butter fat ..	No degeneration	Nearly normal
(*c*)	Butter fat heated and oxygenated 12 hours	Much degeneration	Looked dazed; inco-ordinate; back legs weak; later paralysed

The rate of growth of the three puppies was fairly comparable during the greater part of the experimental period.

Although under the experimental conditions described it is generally possible to obtain the degeneration with cereals, this is not always the case, and the variability made it necessary to seek other means of pursuing the investigation.

It was thought possible that the varying results might depend not only on the early history of the puppies but also on variations in the samples of cereals and especially of the wheat germ. Now the cord degenerations, and to some extent the clinical symptoms, called to mind the pathological conditions of the nervous system associated with human convulsive ergotism. It seemed possible, therefore, that some batches of the wheat germ were ergotized, i.e., infected with the fungus *Claviceps purpurea*, although, since white flour was sometimes associated with cord changes, this explanation was not very likely. Microscopic examination of the wheat germ also gave no support to this supposition. Attempts were, nevertheless, made to produce cord degeneration by adding ergot of rye to the diets of some animals. It seemed indeed probable that if, by the use of ergot, a more certain method of producing demyelination of the spinal cord could be obtained, the problem would be more amenable to study and possibly lead to a clearer understanding of the difficulties.

Reference to the literature dealing with experimental nervous ergotism in animals did not give much prospect of success. Tuczek [10] not only had much experience of convulsive ergotism in man but also made many attempts to produce cord degeneration in animals by adding ergot to the diet. He described the degenerative changes in the cords of patients deceased of nervous ergotism, but never succeeded in producing similar changes in the cords of animals, although he refers to the paralysis, stiffness, weakness and staggering gait produced in dogs which had received 4 to 6 grm. of ergot daily. Writing in 1882, at a time when convulsive ergotism in Germany was an important practical problem, he says of animal experiments, "Positive Sectionsergebnisse in Centralnervensystem bei Ergotismus finde ich in der Literatur nirgends!" Of course, the technical methods used for preparing nervous tissue for microscopic examination were cruder in those days and this may account for the negative results. Whether spinal degeneration in experimental animals such as is described below has been produced by ergot and demonstrated since Tuczek's time, I have not been able to discover.

The following experiments show that nervous ergotism can be induced in dogs under certain dietetic conditions, and that slight alterations in the diet of a specific nature completely prevent the cord degenerative changes even when the same or larger amounts of ergot are eaten

SPINAL CORD DEGENERATION PRODUCED BY ERGOT OF RYE.

In the early experiments, ergot in small quantities (2 to 5 grm. daily) was added to diets deficient in fat-soluble vitamins, but otherwise, so far as was known, complete, and given to puppies of the same litter. Previous experiments in which the cord changes had developed when cereals formed a large part of the diet suggested that the absence of fat-soluble vitamins would also play an important rôle in controlling any influence on the nervous system that ergot might exert.

Before describing the experimental results it may be well to say that, although it is usually an easy matter to feed puppies on diets deficient in fat-soluble vitamins for some months, it is by no means easy to get them to take ergot under these conditions. They may eat up their food containing the ergot for a few days or weeks and then either refuse it or eat their ration incompletely. To meet this situation different devices are necessary varying with the animal in question. Sometimes the ergot is mixed with a small portion of the food and given as a bolus after some of the food has been eaten, sometimes the amount of ergot is reduced, and sometimes it is necessary to suspend giving the ergot for at least a few days. In all cases care and discretion are needed, especially as it is advisable that the animals should not lose weight before the symptoms of nervous ergotism are produced.

The following experiment illustrates the intensification of cord degenerative changes when ergot is added to a diet rich in cereal and deficient in fat-soluble vitamins.

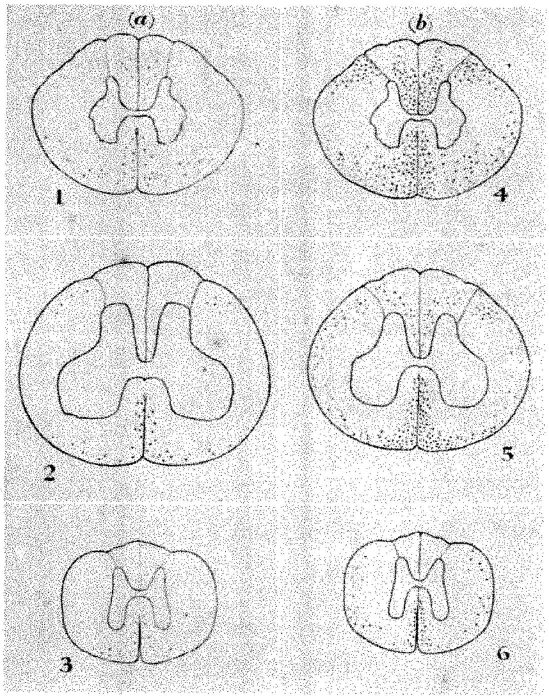

FIG. 2.—Drawings representing the distribution of degenerating nerve fibres as shown by the Marchi technique in the spinal cords of (*a*) and (*b*). (Experiment V.) Drawings 1, 2 and 3 represent sections through the 2nd cervical, 6th cervical and 11th dorsal regions respectively of (*a*) (control diet). Drawings, 4, 5 and 6 represent corresponding sections of (*b*) (ergot). Note the greater amount of degeneration in the cord of (*b*) (ergot), and that there is comparatively little degeneration in the dorsal region.

EXPERIMENT V.

The Production of Degeneration by Ergot.

Age beginning: 9 weeks.

Duration of experiment: About 2 months.

Basal diet: Bread; separated milk powder, 20 grm.; lean meat, 20-10 grm.; peanut oil, 10 grm.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; salt 1 grm.

Animal	Diet variable	Cord degeneration as shown by Marchi staining	Some clinical notes
(*a*)	—	A little degeneration *Ci. A little* degeneration in anterior, antero-lateral columns. A few degenerated fibres in Burdach *Cvi. A little* in anterior and antero-lateral columns. Very little in direct cerebellar, none in Burdach *Dxii. Little* degeneration in anterior column	Fairly active but rather unsteady out of cage
(*b*)	Ergot, 2 g. ..	Much degeneration *Ci. Much* degeneration in anterior and antero-lateral columns, direct cerebellar and Burdach *Cvi. Much* degeneration in anterior column, some antero-lateral and direct cerebellar; little in Burdach *Dxii. Little* degeneration, most in anterior columns	Not very active, and decidedly inco-ordinate

Puppy (*b*) grew steadily throughout the experimental period; (*a*) grew well at first but later lost some weight. The cord changes in these two animals are represented by the drawings of fig. 2.

It will be seen in this experiment that while there is some degeneration in the cord of the control animal, the addition of ergot to the diet has greatly intensified the pathological changes.

In the following experiment not only is the effect of adding ergot examined (*b*), but the stability of the toxic factor in ergot is tested by (1) heating it for eighteen hours at 120° C. (*c*), and (2) boiling it for one hour with 1 per cent. hydrochloric acid (*d*).

EXPERIMENT VI.

The Production of Degeneration by Treated and Untreated Ergot.

Age beginning: 8 weeks.

Duration of experiment: About 4½ months.

Basal diet: Bread, 180 grm.; separated milk powder, 20 grm.; lean meat, 20 grm.; peanut oil, 10 c.c.: orange juice, 3 c.c.; dried yeast, 2 grm.; sodium chloride, 1 grm.

(*a*) had basal diet only.

(*b*) had in addition untreated ergot (2-5 grm. daily).

(*c*) ,, ,, ,, ergot treated 18 hours at 120° C. (2-5 grm. daily).

(*d*) ,, ,, ,, ergot boiled with 1 per cent. HCl for 1 hour (2-5 grm. daily).

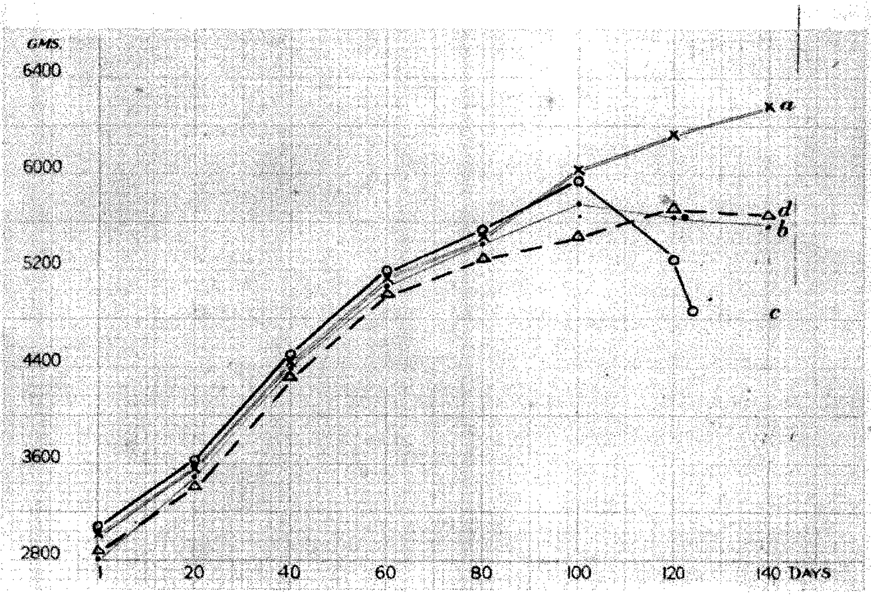

FIG 3.—Weight curve for Experiment VI. *See also* Fig. 4.

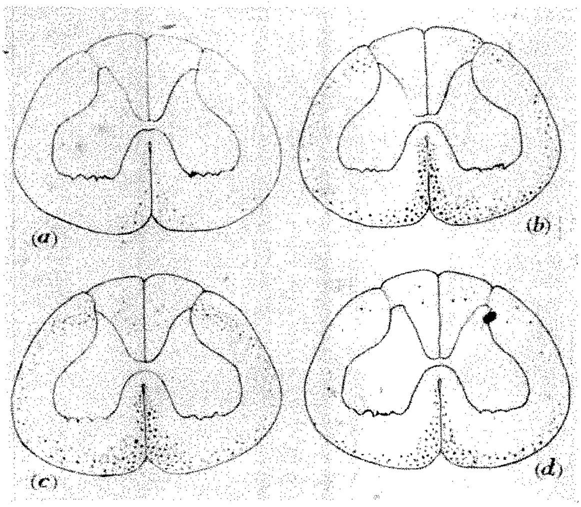

FIG. 4.—Drawings representing the distribution of degenerating nerve fibres as shown by the Marchi technique in the spinal cords at the level of the 6th cervical in dogs (*a*), (*b*), (*c*) and (*d*) of Experiment VI. (*a*) Control; (*b*) ergot; (*c*) heated ergot; (*d*) ergot boiled with dilute acid. Note the increased degeneration produced by ergot whether untreated, heated, or after being boiled with acid. In the latter case the increase is not so great.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(*a*)	—	Little degeneration	Slightly inco-ordinate
(*b*)	Untreated ergot	Much degeneration	Inco-ordinate. Dazed appearance; several fits
(*c*)	Heated ergot	Much degeneration	Inco-ordinate. Very weak and ultimately paralysed. Head movements uncontrolled
(*d*)	Ergot boiled in weak acid	Much degeneration, but rather less than (*b*) and (*c*)	More active than (*c*), but inco-ordinate; dazed appearance

For rate of growth, see fig. 3; for distribution of degeneration, see fig. 4.

This experiment shows not only the increase in cord degeneration produced by ergot, but that the neuro-toxin in ergot is stable to heat and, to a less extent, to boiling with 1 per cent. hydrochloric acid for one hour.

Similar experiments were made on many litters of puppies with the same results,[1] so that it now appeared that a sufficiently reliable means of producing spinal cord degeneration was at hand to allow a more extended study of the problem.

The first point which required investigation was to see whether the cord changes produced by ergot could be prevented by fat-soluble vitamins in the food, for, as mentioned above, demyelination had never been seen in the cords of animals when the diet included cod-liver oil, egg yolk and cabbage, even if the diet was composed largely of cereals.

At this stage of the investigation the method of preparation of vitamin D from ergosterol by irradiation with the mercury vapour lamp had just been announced by Rosenheim and Webster [11], and Windaus and Hess [12], so that it was possible to decide whether vitamin D was the factor in the fat-soluble vitamins which prevented nerve degeneration.

EXPERIMENT VII.

Degenerative Changes produced in the Presence of Vitamin D.

Age beginning: 8 weeks.

Duration of experiment: About 7 months.

Basal diet: Bread, 100-160 grm.: separated milk powder, 20 grm.; lean meat, 20 grm.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; salt, 1 grm.

Each animal also received on the average 3 grm. ergot daily.

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[1] Since this was written, failure to produce the cord changes with ergot has been experienced in one litter of puppies. Although it is the only exception out of about forty experiments, this negative result may be of significance and may indicate that some unknown factor or factors have still to be elucidated.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(*a*)	Olive oil, 10 c.c.	Much degeneration	Head position abnormal. Incoordinate. Discharge from eyes: later ulcer on one eye
(*b*)	Cod-liver oil, 10 c.c.	No degeneration	Normal
(*c*)	Irradiated ergosterol (Vitamin D)	Much degeneration; slightly less than (*a*)	Head position abnormal. Incoordinate. Discharge of pus from eyes

Advanced degeneration, as shown by Weigert's method of preparation, is seen in both (*a*) and (*c*).

This experiment makes it clear that (1) cod-liver oil prevents the neuro-toxic effect of ergot; (2) vitamin D is not the preventive agent.

A casual observation made during this and similar experiments also confirmed the ineffectiveness of vitamin D as a protective agent against ergot. It was noticed that when dogs received ergot, even when eating a diet deficient in fat-soluble vitamins, they did not develop the same intensity of rickets as the animals not getting ergot. It appeared, in other words, that ergot itself contained vitamin D, and so exerted an antirachitic action. This point was followed up, and ergot was shown to contain an appreciable amount of vitamin D (Mellanby, Surie and Harrison [13]), a discovery of interesting significance since, as will be remembered, Tanret [14] first isolated ergosterol, the parent substance of vitamin D, from ergot in 1889. Although ergosterol is very widely distributed in nature, it is rare to find any of it in the activated (vitamin D) form.

Now, since ergot produces spinal cord degeneration, and since it also contains vitamin D as a normal constituent, it did not seem likely that this vitamin in quantities sufficient to prevent rickets would inhibit the toxic action of ergot, a result which has been confirmed in Experiment VII. Since vitamins A and D are both present in cod-liver oil, which has been found to be preventive, it seemed fairly certain that vitamin A would prove to be the protective substance. In the following experiment, different sources of vitamin A were added to the diets in addition to ergot and the effect on the spinal cord studied. It may be stated that the beneficial effects of adding these sources of vitamin A were at once apparent in the general condition of the animals. The difficulty of feeding the ergotized diets greatly diminished, and the animals remained active and healthy looking throughout the experimental period.

EXPERIMENT VIII.

Degeneration Changes resulting from Ergot prevented by Sources of Vitamin A.

Age beginning: 8 weeks.
Duration of experiment: About 4½ months.
Basal diet: Bread; separated milk powder, 20 grm.; lean meat, 20 grm.; peanut oil, 10 c.c.; orange juice, 3 c.c.; dried yeast, 2 grm.; sodium chloride, 1 grm.

In addition all had on the average 2·5 grm. ergot daily.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(*a*)	—	Much degeneration	Inco-ordinate. Several fits; dazed appearance
(*b*)	Butter, 10 g., replacing peanut oil	No degeneration	Active
(*c*)	Mammalian liver oil (vitamin A), 1 c.c.	No degeneration	Active
(*d*)	Cabbage boiled 30 min., 30-50 grm.	No degeneration	Active, but nervous and jumpy
(*e*)	1 egg yolk	No degeneration	Very active

The weight curves of these animals during the experimental period are shown in fig. 5.

Inference from these results:—

(1) Foods rich in vitamin A prevent the ergot from producing spinal cord degeneration.

(2) With vitamin A in the diet, the animals remain active, eat their food well, develop no nervous symptoms and remain in good health.

It may be added that the animals whose diet included vitamin A often had more ergot than other members of the litter because on diets deficient in vitamin A the ergot had more frequently to be omitted from the daily ration.

RYE GERM AND DEGENERATIVE CHANGES IN THE CORD.

Ergot of rye develops as the result of the growth of a fungus, *Claviceps purpurea*, in the embryo of rye. The embryo under these conditions becomes bigger and is ultimately filled with mycelia of the fungus. It was of interest therefore to see whether rye germ itself, free from the fungus, had any action on the spinal cord. It may be noted that, after ergot of rye was found to contain vitamin D (Mellanby, Surie and Harrison) [13], it was discovered that the rye embryo itself also contained some of this vitamin, although in smaller quantities than ergot. In other words, the mycelial invasion of the rye embryo did not produce *de novo* vitamin D but only exaggerated the development of a vitamin originally present in the rye germ. It seemed likely, especially in view of the earlier experiments with wheat germ, that rye germ would also afford evidence of containing the agent abundantly present in ergot of rye which hastens the cord degenerative changes. If this proved to be the case, it would show that the ergotizing of the rye embryo only results in the production of increased amounts of a toxic agent originally present in the rye germ itself. Experiments carried out to test the action of rye germ on the spinal cord proved that this substance does indeed contain the nerve toxin. The following series of tests made on a litter of puppies illustrates the point.

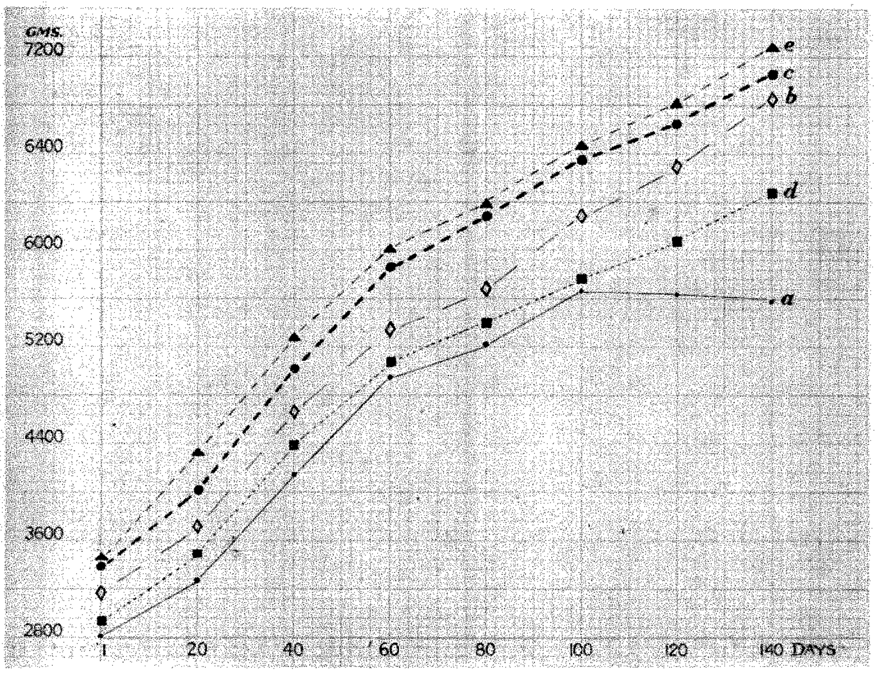

FIG. 5.—Weight curve for Experiment VIII.

EXPERIMENT IX.

The Production of Cord Degeneration by Rye Germ.

Age beginning: 6 weeks.
Duration of experiment: About 5 months.
Basal diet: white flour; separated milk powder, 25 grm.; lean meat, 20 grm.; peanut oil, 10 c.c.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; sodium chloride, 2-4 grm.

(*a*) had in addition petrol ether extract of rye germ equivalent to 20 per cent. of white flour.
(*b*) had basal diet only.
(*c*) had in addition rye germ replacing 20 per cent. of white flour.
(*d*) ,, ,, rye germ heated 36 hours at 120° C., replacing 20 per cent. of white flour.
(*e*) ,, ,, rye germ replacing 20 per cent. of white flour, and 20-50 grm. cabbage boiled ½ hour.
(*f*) ,, ,, rye germ extracted with petrol ether, replacing 20 per cent. of white flour.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Condition as regards rickets	Some clinical notes
(*a*)	Extract of rye germ	Some degeneration	Some rickets	Not normal but ran fairly well
(*b*)	—	Some degeneration	Bad rickets	Slightly inco-ordinate; paralysis in hind legs, from which recovered later
(*c*)	Rye germ	Much degeneration	Some rickets	Hind legs stiff, gait difficult. Head movements abnormal
(*d*)	Heated rye germ	Much degeneration	Rickets ..	Hind legs stiff, abnormal gait. Head movements abnormal
(*e*)	Boiled cabbage	No degeneration ..	Rickets ..	Ran fairly well. No inco-ordination
(*f*)	Extracted rye germ	Very much degeneration (also in Goll's column)	Very bad rickets	Gait abnormal; later hind legs paralysed

The degenerative changes in the cords of these animals are represented in fig. 7, and the changes in weight during the experimental period in fig. 6.

These experiments show that:—

(1) Rye germ contains an agent producing spinal cord degeneration, but probably to a less degree than ergot of rye, since much more rye germ was eaten in these experiments than ergot in similar experiments.

(2) This action of rye germ, like that of ergot, is inhibited by cabbage.

(3) Heating the rye germ for thirty-six hours at 120° C. has not destroyed the substance responsible for this action.

(4) The active agent in rye germ is not removed by petrol ether.

(5) There is no relationship between the amount of cord degeneration and rickets.

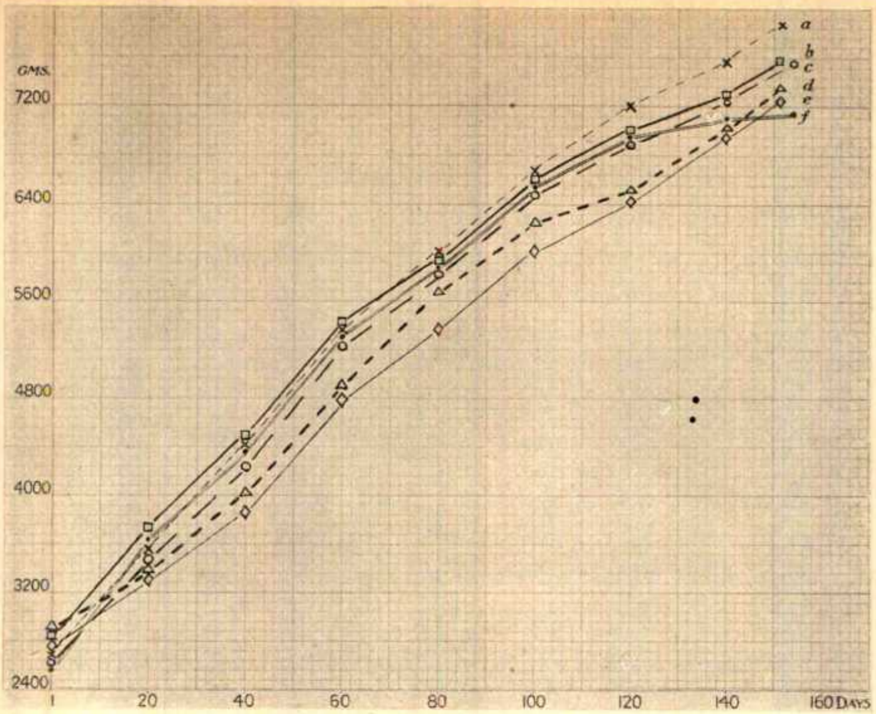

FIG. 6.—Weight curve for Experiment IX. *See also* Fig. 7.

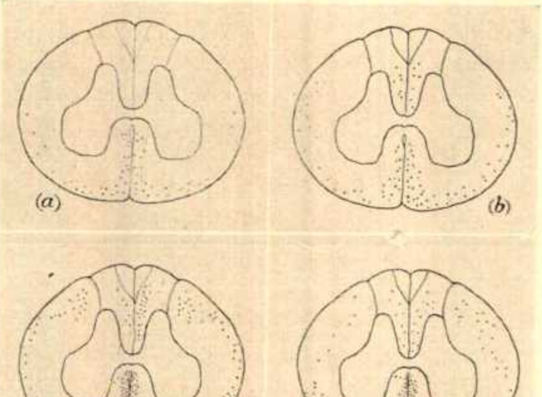

FIG. 7.—Drawings representing the distribution of degenerating fibres as shown by the Marchi technique in the spinal cords at the level of the 5th cervical in (*a*), (*b*), (*c*), (*d*), (*e*) and (*f*) of Experiment IX. (*a*) Petrol ether extract of rye germ; (*b*) control; (*c*) rye germ; (*d*) heated rye germ; (*e*) cabbage (boiled); (*f*) rye germ extracted with petrol ether. Note the greater degeneration produced by rye germ (*c*), heated rye germ (*d*), and extracted rye germ (*f*), while the petrol ether extract of rye germ (*a*) is no worse than the control. The addition of cabbage (*e*) has prevented all degeneration.

The Prevention of Cord Changes by Vitamin A when the Diets are Rich in White Flour and Wheat Germ.

It has been previously shown that: (1) The degenerative changes in the spinal cord produced by diets rich in white flour and wheat germ are prevented by butter but not by olive oil; and (2) the changes produced by ergot are prevented by vitamin A. It now remained to see whether the protective effect of butter against cereals, which it lost on being heated and oxidized (see Exp. 2), was also due to its vitamin A content.

In the following experiment (Exp. 10), the relative defensive effects of irradiated ergosterol (vitamin D), and mammalian liver oil (vitamin A), were compared when the cereal moiety of the diet consisted of 75 per cent. white flour and 25 per cent. wheat germ.

Experiment X.

The Relative Effects of Vitamins A and D on Cord Degeneration produced by Cereals.

Age beginning: 7 weeks.
Duration of experiment: About 4 months.
Basal diet: Separated milk powder, 20 grm.; lean meat, 20-10 grm.; peanut oil, 10 c.c.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; salt, 2-3 grm.

(*a*) had 75 per cent. white flour, 25 per cent. wheat germ.
(*b*) ,, 75 ,, ,, ,, 25 ,, ,, ,, and irradiated ergosterol.
(*c*) ,, 75 ,, ,, ,, 25 ,, ,, ,, and vitamin A (mammalian liver oil

Animal	Diet variable	Cord degeneration as shown by Marchi staining	Some clinical notes
(*a*)	—	Some degeneration, especially in anterior and antero-lateral columns	Abnormal gait; later hind legs paralysed; had fits
(*b*)	Irradiated ergosterol (vitamin D) 0·05-0·1 c.c	Rather more degeneration than in (*a*), especially in anterior and antero-lateral columns	Abnormal gait; hind legs stiff and head movements uncontrolled. Could just walk at end of experiment; had fits
(*c*)	Vitamin A oil, 1 c.c. (from mammalian liver)	No degeneration	Fairly active throughout experiment; no inco-ordination

(*b*) and (*c*) increased steadily in weight throughout the experimental period; (*a*) grew well at first but later lost weight.

This experiment shows clearly that vitamin A and not vitamin D prevents the cord degeneration when white flour and wheat germ are the cereals eaten.

Experiment XI shows that the cereal effect can be antagonized by cabbage. Both animals received oatmeal as the cereal of the diet and vitamin D in the form of irradiated ergosterol.

EXPERIMENT XI.

The Prevention by Cabbage of Cord Changes produced by Cereals.

Age beginning: 7 weeks.
Duration of experiment: About 3 months.
Basal diet: Separated milk powder, 20 grm.; lean meat, 20-10 grm.; peanut oil, 10 c.c.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; salt, 3 grm.; irradiated ergosterol (vitamin D), 0·1 c.c.
(*a*) had 80 per cent. oatmeal and 20 per cent. ground wheat germ.
(*b*) ,, ,, ,, ,, ,, ,, 20 ,, ,, ,, ,, and 50 grm. cabbage boiled half an hour.

Animal	Diet variable	Cord degeneration as shown by Marchi staining	Clinical notes
(*a*)	—	**Fair amount of degeneration, especially in Cii, anterior, antero-lateral and direct cerebellar regions**	**Hind legs stiff; later gait incoordinate**
(*b*)	**Cabbage boiled ½ hour**	No degeneration	**Gait normal**

Both animals grew well until towards the end of the experiment and then lost weight.

It now seemed established that the degenerative changes in the cord could be entirely prevented by vitamin A both when the diet contained ergot and when rich in cereals.

Since the liver is a storehouse of vitamin A, it became a matter of interest to see what happened to these stores when diets respectively rich and poor in this substance were eaten. Did they disappear when the diet was deficient in this respect and did their absence from the liver determine the development of the cord changes? In order to decide this point, the livers of many animals with and without symptoms of cord degeneration were examined for vitamin A. The technique employed was as follows: 20 grm. of liver were heated on a water bath with alcoholic potash; the alkaline mixture was thrice extracted in a separating funnel with ether; the ether was distilled off, care being taken to drive off any moisture, and the colour test of Carr and Price [15], using a chloroform solution of antimony trichloride, was applied to the residue. The intensity of the blue reaction was estimated by means of a Lovibond tintometer (Rosenheim and Schuster pattern), and recorded in blue units. When this method is used under standard conditions, it is generally believed to give a fairly accurate indication of the amount of vitamin A present in the liver. In the figures recorded in this paper a blue unit is that amount of substance which, dissolved in a 1-cm. cube and treated with antimony trichloride, produces a tint equivalent to one Lovibond unit when viewed through a depth of 1 cm. To convert this figure into the blue units which will probably be officially adopted by the British Pharmacopœia, it should be multiplied by 2·2.

No degenerative changes were found in the cords of these experimental animals except when the liver was denuded of vitamin A. This does not mean that absence of vitamin A from the liver always results in cord degeneration, for, as will be seen later (p. 267), there are cases when, for instance, carotene is a constituent of the diet, where there may be no vitamin A in the liver and yet no degenerative changes in the cord. There are also a few exceptional unexplained cases when there is little or no vitamin A or carotene in the food, no vitamin A in the liver, and yet no cord degeneration. The point that seems clear is that, if there is a store of vitamin A in the liver in these animals, cord changes are not found, and if cord changes are found there is no vitamin A in the liver unless this is given after the changes have developed.

Having shown that vitamin A prevents not only cereals but also ergot from exerting its neurotoxic action, it was necessary to see whether this preventative effect could also be obtained with carotene. Parenthetically it may be stated that when the above-described experiments were made the fact that the vitamin A action of cabbage was due to carotene had not been suggested. The relation of vitamin A to carotene has been under discussion for many years, since Steenbock and Boutwell [16] drew attention to the fact that the colouring matter of foods was often related to their vitamin A content. It was at first thought that carotene might actually be vitamin A. This was soon shown not to be the case, for preparations made from cod-liver oil, although containing abundant vitamin A according to biological tests, were devoid of carotene. The problem was brought to the fore again in 1928, by Euler, Euler and Hellström [17], who found that for growth in young animals carotene could be substituted for vitamin A. This was denied at first by Dulière, Morton and Drummond [18], but confirmed by Moore [19], and by Collison, Hume, Smedley-Maclean and Smith [20]. A further development took place in 1929, when Green and E. Mellanby [21] found that the anti-infective action of vitamin A could be similarly exerted by carotene. Of course, none of these investigations settled the problem as to whether pure carotene was the active agent and the experience of investigators on the relation of cholesterol, ergosterol and ultra-violet irradiation to vitamin D, has made many hesitate to declare that carotene itself acts like vitamin A and that its effect is not due to some vitamin A impurity. The general trend of results, however, especially those of Euler and his associates [22], suggests that carotene, a chemical substance associated with vegetable life and especially with green vegetables and carrots, has specifically the biological properties of vitamin A. T. Moore [23] has indeed brought forward evidence which suggests that it is the parent substance of vitamin A, and that on giving carotene to animals vitamin A is produced and stored in the liver. In order, therefore, to test the relationship between vitamin A and carotene from quite a different angle, experiments were made to see whether carotene could also prevent the degenerative changes in the spinal cord produced by cereals and ergot.

In the following and other similar experiments, carotene, supplied by the British Drug Houses, was tested to see whether it could prevent the degeneration produced by ergot. Carrots, the richest known source of carotene among vegetable substances, were also tested.

EXPERIMENT XII.

The Prevention of Cord Degeneration by Carotene.

Age beginning: 9 weeks.
Duration of experiment: About 2 months.
Basal diet: White flour, 130 grm.; separated milk powder, 20 grm.: lean meat, 10 grm.; peanut oil, 10 c.c.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; sodium chloride, 3 grm.; irradiated ergosterol (vitamin D), 0·1 c.c.

Animal	Diet variable	Cord degeneration as shown by Marchi staining	Vitamin A in liver at P.M. as tested by $SbCl_3$	Some clinical notes
(*a*)	Carotene, 5 mg... Ergot, 2 grm. ..	No degeneration ..	No vitamin A ..	Fairly active. No inco-ordination
(*b*)	Carrots, 25 30 grm. Ergot, 2 grm.	No degeneration ..	No vitamin A ..	Fairly active
(*c*)	Butter, 10 grm... Ergot, 2 grm.	No degeneration ..	Some vitamin A (1 5 Blue Units per grm.	Fairly active. Normal gait
(*d*)	—	No degeneration ..	No vitamin A ..	Fairly active
(*e*)	Ergot, 2 grm. ..	Much degeneration.	No vitamin A ..	Very inco-ordinate. Later lost weight and became weak. Eyes not quite normal

The rate of growth was good in all cases, but (*e*) lost weight later in the experiment. Fig. 8 represents drawings of sections of different levels of the spinal cord of (*e*), the only animal of this experiment developing cord degeneration. From these drawings the relative distribution in different parts of the spinal cord can be seen.

It is evident that in animals receiving ergot, cord degeneration was prevented by carotene itself and by carrots which contain carotene, and by butter, which contains both vitamin A and carotene. No degeneration was found in (*d*), the control animal, which was given neither ergot nor a protective agent. In addition to these facts, there are several other

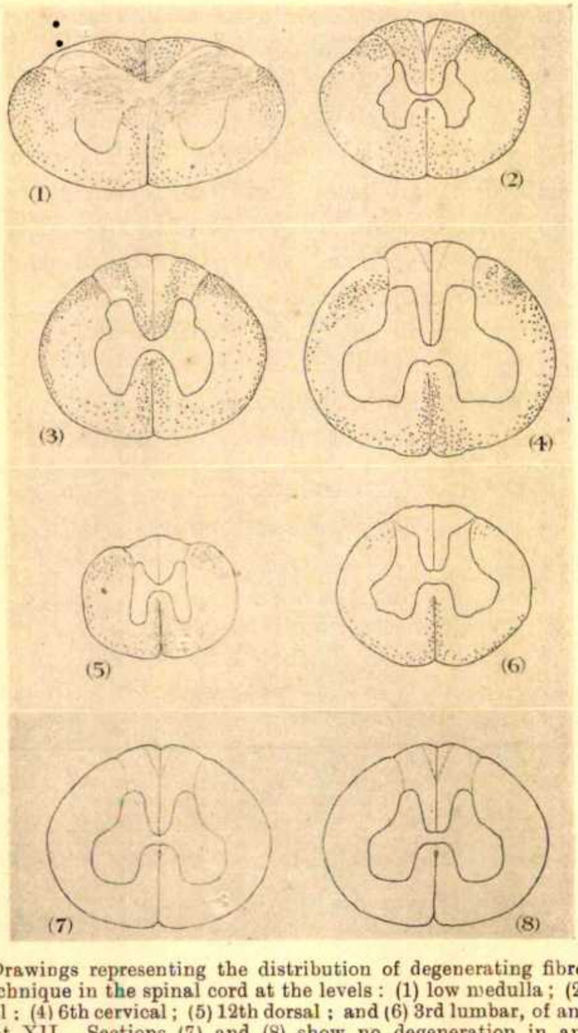

FIG. 8.—Drawings representing the distribution of degenerating fibres as shown by the Marchi technique in the spinal cord at the levels : (1) low medulla ; (2) 1st cervical ; (3) 3rd cervical ; (4) 6th cervical ; (5) 12th dorsal ; and (6) 3rd lumbar, of animal (*e*) (ergot) of Experiment XII. Sections (7) and (8) show no degeneration in animals (*a*) and (*c*) (cervical region), which received carotene and butter respectively.

points of interest about this series of animals. The first is the rapidity with which the cord degeneration can be brought about by ergot under favourable conditions. The feeding period only lasted seven and a half weeks and yet in (*e*), where there was no protective agent in the diet, extensive nerve degeneration developed in all the regions examined, including the medulla.

The second point of interest concerns the vitamin A stores in the liver. These were probably very small at the beginning, otherwise (*e*) would not have reacted so quickly to ergot. It will be further noticed that even when carotene and carrots were ingested there was no vitamin A observable in the liver by the colour reaction of Carr and Price. This fact opens up several questions of interest which, however, can only be touched upon here. It was stated earlier that the store of vitamin A in the liver of the experimental dogs has apparently to be used up before spinal cord degeneration develops. It might be inferred, therefore, that when the vitamin A stores are used up, especially when ergot is in the diet, the nerve degeneration would be evident. This does not seem to happen when carotene is in the diet. It may then be asked why, if carotene is the precursor of vitamin A in the liver, there was no vitamin A in the livers of (*a*) and (*b*), which received carotene and carrots respectively. This question cannot yet be answered. Possibly, if larger doses of carotene or carotene-containing substances had been given to these animals, a store of vitamin A would have been produced in the liver. Apparently carotene can act immediately after absorption from the alimentary canal either, as seems probable, directly, or after conversion to vitamin A, and thereby protects the nervous system from the toxic action of ergot. An analogous phenomenon is seen when carotene acts either prophylactically or curatively in bacterial infection in animals (Green and Mellanby [21]). Animals may be fed on diets deficient in vitamin A and so lose their stores. If carotene in sufficient quantity is now given, no infective lesions will develop, or if they have developed, will disappear, and yet the livers will often be found post-mortem to contain no vitamin A. Here, as in the degeneration experiments, although no vitamin A can be found in the liver, carotene exerts its anti-infective action and prevents epithelial hyperplasia.

Moore's results [23], in which he got evidence of the change of carotene to vitamin A in rats, have already been referred to above. The curious thing about experiments of this nature, as my colleague Green and I [21] have previously pointed out, is that surprisingly large quantities of carotene have to be given to these animals before vitamin A can be found in the liver—much more, in fact, than is necessary to clear up all signs of vitamin A deficiency.

The Antagonism between the Nerve Toxin and Vitamin A and Carotene.

The foregoing results and others of a similar nature show that demyelination of the cord fibres is controlled by at least two factors—a positive harmful influence and the absence of a defending chemical mechanism—and this clarifies the problem to some extent, although of course it leaves much obscure.

The double mechanism may well explain, for instance, the difficulties earlier workers had in producing demonstrable cord changes in nervous ergotism, for at that time not only were vitamins unknown but the protective action of specific food elements was unheard of.

A second difficulty, which is also at least partially explained, is that referred to above (p. 251) in connection with the original experiments in which inconsistent results were obtained in different litters when cereals alone were employed. It appears that the variation in the results must have depended to some extent on the initial stores of vitamin A in the puppies of the different litters at the beginning of the feeding period. The liver is the main organ in which vitamin A is stored and the amount stored in this organ in different animals varies greatly. Sometimes it may be as high as 1,900 blue units per gramme of liver and sometimes it is almost negligible in amount or even absent. The amount in the liver depends on the amount of vitamin A and carotene included in the animal's food. If, for instance, puppies have been fed during the pre-experimental periods on diets containing cod-liver oil, butter and egg-yolk, their livers are very rich in the substance. The relation of the storage of vitamin A and the development of nervous lesions was investigated and it was found that when the pre-experimental diet was rich in vitamin A the time required for the production of nervous symptoms was lengthened. Thus the development of symptoms depends not only on the deficiency of vitamin A and carotene from the diet but also on the time it takes for the stores of the vitamin in the body to be used up. As might be expected the time of denudation varies greatly according to the original stores. In some cases this period may be several months and in others a few weeks. It is advisable, therefore, in experiments of this type to control the pre-experimental diet in order to ensure as far as possible similar reactions to the experimental feeding in point of time and intensity. There is also some evidence which suggests that good feeding in the sense described, if continued long enough, may confer immunity against the neurotoxins for a long time after the liver vitamin A stores are completely denuded.

The protective action of carotene on the nervous system supports the suggestion that this substance and vitamin A are physiologically similar although not identical chemically. The action of carotene must also be taken into account in considering the effect of cereals of which it is sometimes a constituent. For instance, apart from the influence of the varying stores of vitamin A in the livers of different litters of pups, referred to above, it seemed possible that the irregularity of results in the cereal experiments might be influenced by (1) the presence of traces of carotene in the samples of wheat germ, or by (2) varying amounts of toxic factor in the different samples, or both. Examination of wheat germ for carotene revealed that there is a certain amount of this substance present and it is probable that it prevents in some degree at least the spinal degeneration. My colleague H. N. Green has estimated that 100 grm. of wheat germ contained about 1 mg. of carotene. Whether this amount varies in different specimens, and whether the variation is of significance in explaining the results obtained, is not known. One milligram increase in carotene intake daily would certainly modify the experimental results. It is of interest to note that rye germ was found by Green to contain only half the carotene found in wheat germ.

Although the cereals have not been systematically investigated in this respect, experiments were made in which yellow and white maize formed the cereal element of the diet. Yellow maize has for many years been given in diets as a source of vitamin A (Steenbock and Boutwell [16]), but this quality is almost certainly due to its carotene content, which is large for a cereal. White maize, on the other hand, contains little or no carotene. It would be expected, therefore, that it would be more difficult to produce cord degeneration in dogs when the cereal of the diet consisted of yellow rather than white maize. This is certainly the case, and in preliminary experiments it has not only been impossible to produce the degenerative changes with yellow maize, but even where ergot was added to the diet there was sufficient carotene in the yellow maize to prevent the ergot neurotoxic action (see Exp. XIII below). The difference in the condition of animals when yellow or white maize is added respectively to diets otherwise deficient in vitamin A and carotene is great and, so far as is known, this difference is due entirely to the carotene in the yellow maize. This point will be referred to again in the discussion on the possible bearing of these results on pellagra.

The following experiment illustrates the protective effect of yellow maize against ergot and, in addition, shows that when white maize forms the cereal basis of a diet deficient in vitamin A and carotene, spinal cord degeneration develops:—

EXPERIMENT XIII.

The Relative Effects of White and Yellow Maize.

Age beginning: 10 weeks.
Duration of experiment: About 3 months.
Basal diet: Separated milk powder, 20 grm.; lean meat, 20-10 grm.; peanut oil, 10 c.c.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; salt, 3 grm.

Animal	Diet variable	Cord degeneration as shown by Marchi staining	Some clinical notes
(*a*)	White maize. Irradiated ergosterol.	Some degeneration	Quiet and dazed; stupid appearance. Gait not normal. Ulcer on eye
(*b*)	White maize. Irradiated ergosterol. Ergot, 2 grm.	Much degeneration; little anterior and antero-lateral; big patch in Burdach	Legs spastic; inco-ordinate. Head positions abnormal; looks stupid
(*c*)	Yellow maize, Irradiated ergosterol. Ergot, 2 grm.	No degeneration	Normal

"CURATIVE" EXPERIMENTS WITH SUBSTANCES CONTAINING VITAMIN A AND CAROTENE.

It has been shown that substances containing vitamin A, such as butter, egg yolk, mammalian liver oil and also carotene and carotene-containing foods including cabbage and carrots, prevent ergot and other toxins from attacking the nervous system and from producing nerve degeneration in the spinal cord. The problem then arises as to what happens if the animals are given ergot with a diet deficient in vitamin A and carotene until signs of nerve degeneration develop and are then given these substances in abundance? In other words, are vitamin A and carotene curative as well as protective in their action? There is definite evidence that the clinical condition tends to clear up rapidly under these conditions, though the degree of improvement naturally depends on the extent of the initial lesion. The immediate effect is often astonishing even when the animal has been paralysed for a long time. In a week or two animals with weak or even paralysed hind legs become active once more. At first the activity brings out more prominently the inco-ordination and the animals run about with an intoxicated gait. Usually this diminishes greatly and in some cases the animals may later appear almost normal. Presumably further degeneration ceases on giving the additional vitamin A or carotene, and the fibres already showing degeneration are gradually absorbed.

One animal which, although it had been unable to stand for some months, and showed great spasticity especially when held in the standing position, was given vitamin A prepared from mammalian liver. After three weeks the animal could stand but was very inco-ordinate when it attempted to walk. Two months of vitamin A feeding resulted in a very active animal but there was still some inco-ordination which, however, further diminished by the end of the experiment three months later, but, as might be expected, gait never became normal. Examination of the spinal cord by Marchi's method showed complete absence of fibres with demyelination. Areas of sclerosis were found by Weigert's method of staining, indicating that the degenerating fibres had disappeared and had been replaced by neuroglia. Presumably other tracts took on the function of the injured ones and the animal relearnt to walk more or less normally.

The cord of another animal which had received 5 mg. of carotene daily for seventeen days after the development of severe ergot symptoms was kindly examined histologically by Dr. Perdrau. In this period the animal made great clinical improvement but the cord still showed a large number of degenerating fibres when stained by Marchi's method, and areas of more complete degeneration when prepared by Weigert's method.

The first rapid improvement which follows the giving of vitamin A or carotene, especially as regards activity, may depend upon some action of these substances on the muscle itself, but the gradual and continuous improvement which develops later is undoubtedly due to a better functioning of the central nervous system itself. It is clear that vitamin A and carotene not only prevent the cord changes produced by ergot but that they exert a "curative" effect after development of these changes in the sense that great clinical improvement with increased activity and diminished inco-ordination takes place after their administration. In course of time all active degeneration of the nerve fibres in the cord disappears and demyelination demonstrable by Marchi's technique can no longer be found.

There are few more striking effects in animal nutrition than the improvement brought about by the daily addition of 5 mg. of carotene to an animal suffering from severe nervous ergotism.

Clinical Condition and Degeneration Changes in the Cord.

The main clinical symptoms in the affected dogs are spasticity, especially of the hind limbs, and inco-ordination in walking and running, which may, however, especially if the experiment is prolonged, be masked by weakness. Often the head is held on one side and the ears are awry, giving the animal a weird appearance. In the early stages the animal usually has a pica and runs about apparently looking for suitable food and in so doing attempts to eat anything it comes across. At a later stage it seems incapable of fixing its attention for more than a moment and lurches about with no apparent object, and looks stupid. At a still later stage weakness, especially of the hind legs, becomes more apparent and the animal remains standing, often with legs apart and

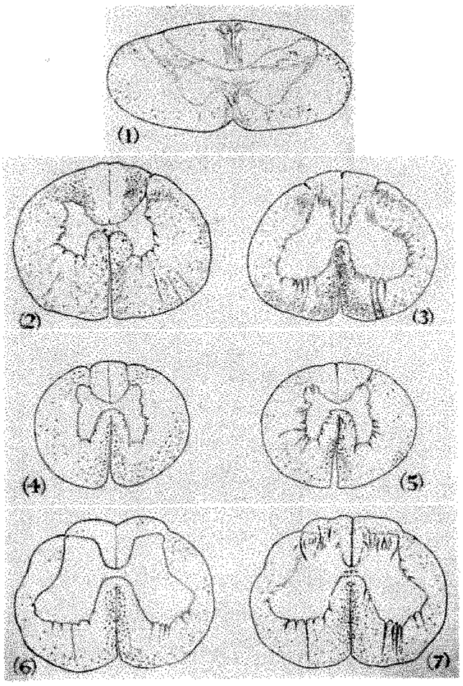

Fig. 9.—Drawings representing the distribution of degenerating fibres as shown by the Marchi technique at different levels of the spinal cord of an animal which had received ergot and no vitamin A or carotene. The levels represented are: (1) medulla; (2) 2nd cervical; (3) 6th cervical; (4) 2nd dorsal; (5) 11th dorsal; (6) 3rd lumbar; (7) 4th lumbar. Note the differences in distribution of degenerating nerve fibres at the different levels, especially the variations found in the posterior columns.

spastic. After passing through a stage when it prefers to sit and make no effort to move, it may become paralysed. The eyes often develop pathological changes and the inco-ordination then appears more prominent owing to defective vision. At any time convulsions may occur.

The difficulty of describing in summary the positions of degeneration arises more particularly from the fact that often the amount of degeneration in the same tracts varies to some extent from level to level and degeneration may be evident in a tract at two levels in the cord whereas at an intermediate level little or no degeneration may be found in the corresponding area.

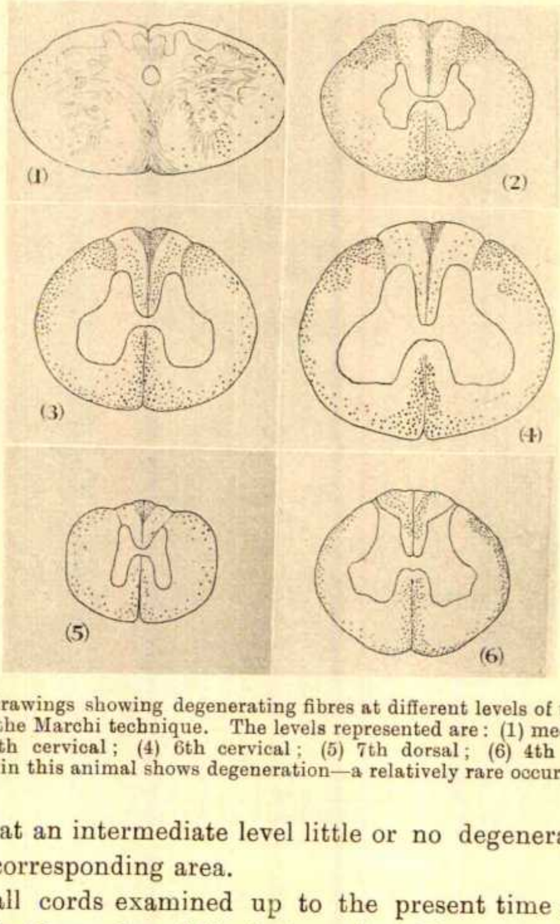

FIG. 10.—Drawings showing degenerating fibres at different levels of the spinal cord as prepared by the Marchi technique. The levels represented are: (1) medulla; (2) 2nd cervical; (3) 4th cervical; (4) 6th cervical; (5) 7th dorsal; (6) 4th lumbar. The column of Goll in this animal shows degeneration—a relatively rare occurrence.

Thus, of all cords examined up to the present time and showing degeneration in the region of the first cervical, 72 per cent. of cases had degenerated fibres in the column of Burdach, whereas in the same cords in the region of the sixth cervical only 52 per cent. showed degeneration in this tract. Again in the direct cerebellar tract: 44 per cent. of sections of the first cervical region showed degeneration; 62 per cent. of sections of the third cervical region showed degeneration; 36 per cent. of sections of the sixth cervical region showed degeneration. This irregularity in the appearance of degeneration is apparently a condition also found in the demyelinated fibres of sub-acute combined degeneration associated with pernicious anæmia.

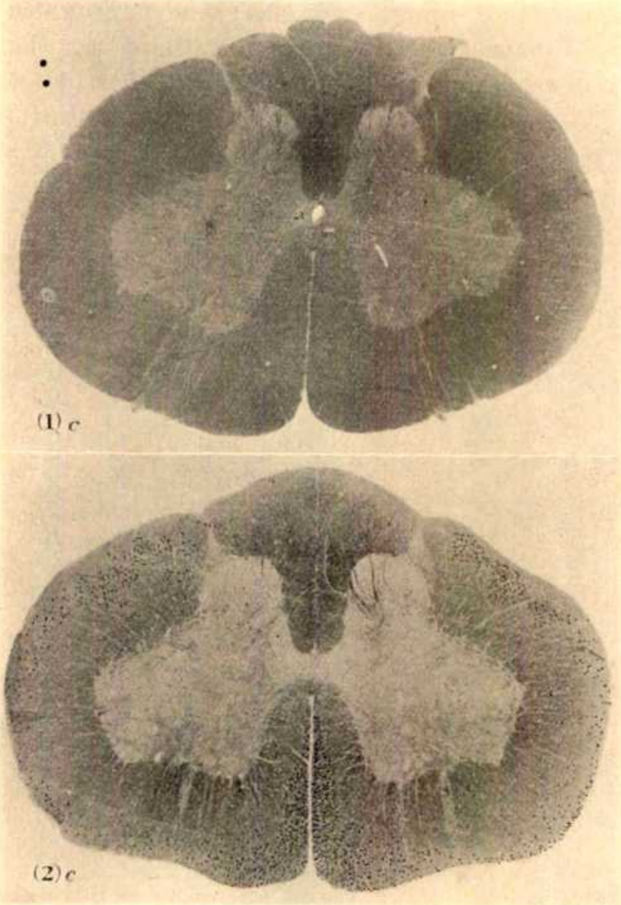

FIG. 11.—Photomicrographs of sections stained by Marchi technique of animals (*c*) and (*e*) of Experiment XII at a level of the 6th cervical. Note the absence of all degeneration from (1) (carotene plus ergot) and the abundant degeneration in (2) (ergot). (Retouched.)

Some other points as regards areas of degeneration demonstrated in these experiments by the use of Marchi and Weigert stains may be mentioned :—

(1) Degenerative changes are more prominent in the cervical than in the lumbar region (fig. 9).

(2) The anterior columns are most affected whichever region of the cord is investigated (fig. 10).

(3) The anterior columns (represented in the human cord by the direct pyramidal tract, a tract said not to be present in the cord of the dog), the antero-lateral tract, especially superficially, the column of Burdach, and the direct cerebellar tracts are the positions most commonly associated with degeneration. In the direct cerebellar tract, the degenerated fibres are often found near the surface, but sometimes they are deeper, away from the surface, whereas sometimes both areas are affected. The fibres of Goll's column are not often affected.

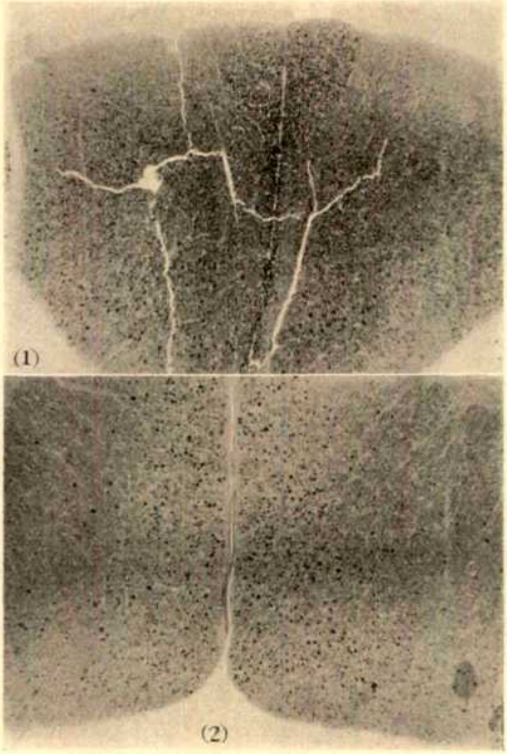

FIG. 12.—Photomicrographs showing cord degeneration by the Marchi technique in (1) posterior columns (note the degeneration in Goll's column) and (2) anterior columns.

(4) The crossed pyramidal tracts are usually but not always free from degeneration.

(5) The indications are that the ascending fibres of the cord are more particularly picked out, including those passing to the cerebellum.

Areas of degeneration at different levels in the cord can be seen in figs. 9 and 10. The point of interest of fig. 9 is that it shows degeneration in the column of Goll, a rare occurrence in these experiments.

The spasticity of the limbs suggested that the upper motor neurone would show extensive degeneration, but this does not appear to be the case. It seems possible that the spasticity may ultimately be related to changes in the cord and mid-brain concerned with posture but nothing definite can be said yet on this point. Neither the upper parts of the brain nor the mid-brain has yet been fully examined histologically. The fits, stupid appearance, inco-ordination and loss of balance suggest that further extension of the examination to the upper parts of the central nervous system will show degenerative changes.

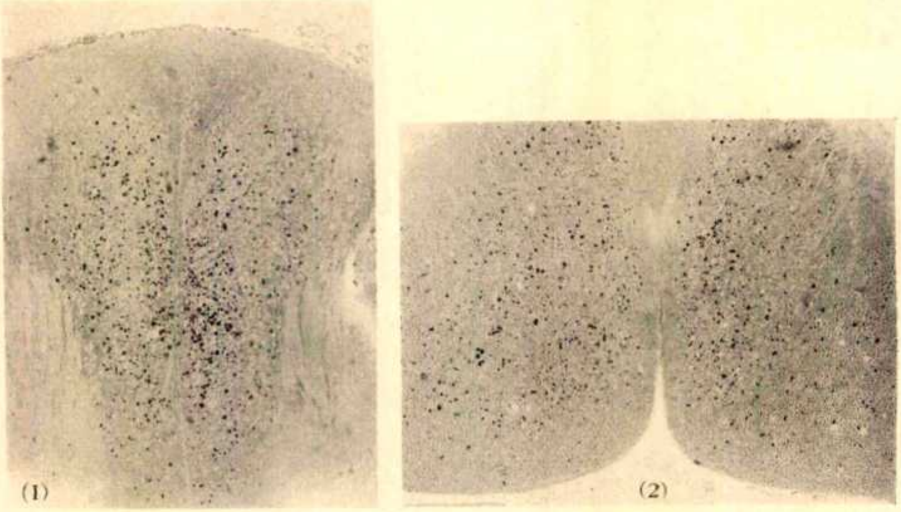

FIG. 13.—Photomicrographs of the spinal cord at the level of the 1st cervical, stained by Marchi technique. (1) Posterior columns (degeneration in Burdach only, the usual occurrence) and (2) anterior columns.

The changes in the cord do not seem to be accompanied by any cell invasion or other indication of an inflammatory nature. Neuroglial overgrowth in the positions of degeneration is not great but the blood-supply to these areas appears in Weigert-stained sections to be increased. Probably the relative smallness of sclerotic growth is due to the shortness of the experiments. In longer experiments, e.g., thirty-one weeks, larger areas of degeneration can be seen when the cord is stained by Weigert's method.

The distribution of cord degeneration suggests strongly that the fibres going to the cerebellum are involved. The clinical condition (inco-ordination, loss of balance) also agrees with this suggestion.

The relation of the clinical condition to the cord changes is not easy to interpret, partly because of the interference of other factors and partly because of the obvious difficulty of investigating sensory changes in animals. For instance, muscular weakness is undoubtedly to be partly explained by the intrinsic failure of the muscle and may be independent of nervous defect. Again, pathological changes in the eyes are often found which interfere with vision. Sometimes the eyes are affected by xerophthalmia due to a deficiency of vitamin A, but in dogs

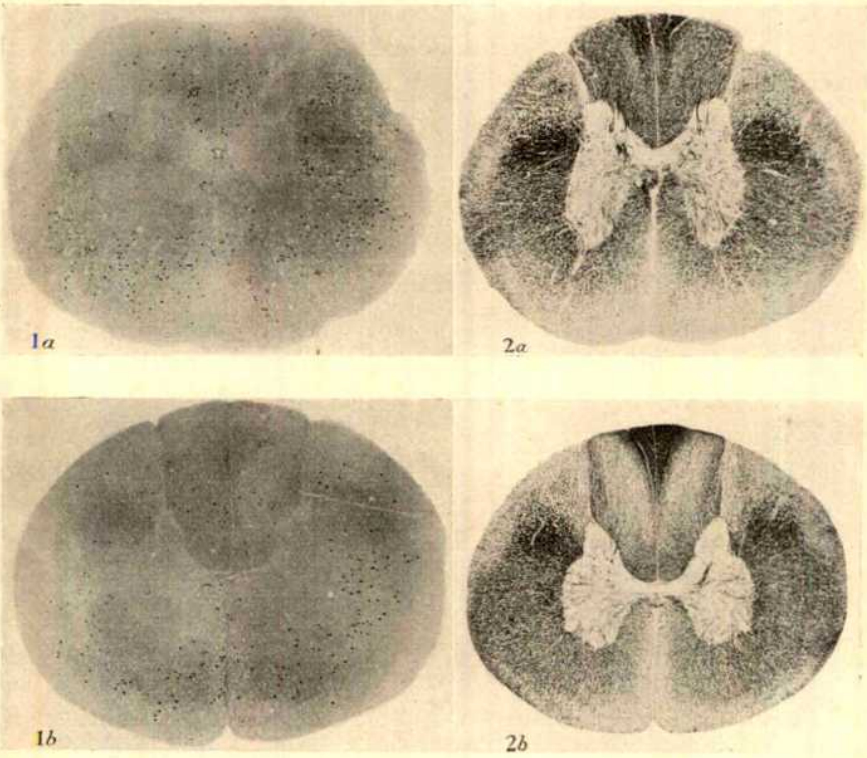

FIG. 14.—Photomicrographs of the 2nd and 4th cervical regions of one cord showing degeneration by (1) Marchi and (2) Weigert technique, respectively, after about five months of ergot feeding (without vitamin A or carotene). 1 (*a*) and 2 (*a*) are photographs of the 2nd cervical level; 1 (*b*) and 2 (*b*) of the 4th cervical level.

receiving a diet deficient in this vitamin and containing ergot another inflammatory condition of the eyes, often affecting the conjunctiva and becoming in some cases suppurative, is sometimes seen. Together with the conjunctivitis, a vascularized keratitis may develop. (I am indebted to my colleague, Mr. Wellwood Ferguson, for examining the eyes of some of these animals.) In one group with vascularized keratitis examined by him, no organisms were grown from the pus exuding from the eyes). This suppurative condition of the conjunctiva and cornea is rarely seen in experimental dogs except when ergot is given, and no doubt this substance plays a specific part in its development. In view of the well-known relation of vitamin A to hemeralopia, it is also probable that the vision is affected more centrally in many of these animals. An attempt to disentangle the relation of all these pathological changes to the behaviour of the animals is now being made.

THE POSSIBLE BEARING OF THE RESULTS TO NERVOUS DISEASE IN MAN.

The question now arises as to what bearing these experimental results have on human nervous diseases.

Convulsive ergotism.—The above described results are probably of immediate application to the condition of convulsive ergotism in man which appears occasionally in epidemic form in rye-eating countries. They suggest an explanation as to why such epidemics only appear in times of famine and poverty. The explanation usually given is that people eat more ergotized bread during such periods, but this, though true in itself, probably only plays a comparatively small part in the problem. If the people eating ergotized rye bread also received sufficient of the protective foods such as green vegetables, butter and egg-yolk containing vitamin A and carotene, no nervous symptoms would, on the basis of the experiments, be expected to develop. Since spinal cord degeneration has been found to develop in many animals in the absence of vitamin A even when no ergot was included in the diet, it is probable that in human beings also the pathological changes ascribed to ergot may in some cases be due to unergotized rye bread itself when eaten under conditions of restricted protective foods. Another point of interest is that in epidemics of nervous ergotism some members of a family may be attacked and others escape. The reason for this indiscriminate picking out of individuals may be related to the reserves of vitamin A in the livers of the individuals. In my experience with dogs, I have found degenerative changes in the spinal cord only when the liver was depleted of vitamin A. The periods required for this depletion vary greatly in animals according to the other factors of the diet and to the amount of vitamin A initially stored, and the latter will be a crucial factor in the time of onset of nervous ergotism in individuals.

If the experimental results can be directly extended to human nervous ergotism, as seems likely, they indicate that not only can the condition be prevented by supplying foods containing vitamin A and carotene, but also that when the condition has developed immediate improvement in health will follow the administration of such foods. Complete cure is unlikely since nerves in the central nervous system cannot regenerate, and the extent to which function returns will depend on the extent and intensity of the nerve degeneration at the beginning of treatment, but in animals at least the "curative" effect as indicated by clinical improvement is very great.

Pellagra.—The cord changes produced in some of the experimental animals are so similar to those associated with pellagra in man, and the mode of producing them is so closely related to the conditions conducive to this disease that it is difficult to avoid the assumption that they throw new light on its ætiology. Like convulsive ergotism, pellagra is a disease of poverty and is often but not exclusively found among maize-eating populations, and especially in the southern part of the United States. Two types of pathological change are found in this disease—one affecting the skin, especially the hands and parts of the body exposed to sunlight, and the second affecting the nervous system and producing both cerebral and cord symptoms. It is natural to suppose that the skin changes are secondary to those of the nervous system, and indicate a release of the trophic control of the affected skin areas. On the other hand, the two types of change are sufficiently dissociated in many cases as to suggest that two mechanisms are responsible—the breakdown of one resulting in the skin changes and of the other the nervous changes. Experimental evidence also supports the suggestion of a double mechanism which may, however, in some way at present unknown work in harmony. Since the work of Goldberger and Tanner [24] it has been widely accepted that pellagra is a deficiency disease due to the absence from the diet of sufficient vitamin B_2 (or vitamin G of the U.S.A.). This conclusion depended on the curative effects on the skin lesions of pellagrins produced by a series of substances such as yeast, meat and milk. The group of foods having this curative effect was such as to preclude the action being due to a then known vitamin, and the hypothetical active substance was called the P-P, or pellagra-preventing, factor. Confirmation of this work from another angle seemed to be forthcoming in animal experimental work. The condition known as "black tongue" in dogs was regarded by Goldberger, Wheeler, Lillie and Rogers [25] as analogous to pellagra in man and reacted to the pellagra-preventing factor as did pellagra itself. Goldberger and Lillie [26], and also Chick and Roscoe [27], extended the investigations to rats and in consequence of the skin lesions produced in rats by diets deficient in vitamin B_2, Chick and Roscoe called this substance the anti-dermatitis factor. Recent work described by Aykroyd [28] has, however, led to some doubt as to the identity of vitamin B_2, in so far as the properties of this substance have been elucidated by rat-feeding experiments, and the P-P factor and the problem must still be regarded as unsettled.

Now the results described above suggest that vitamin A or carotene also plays a part in the prevention of pellagra or at least in its nervous manifestations. There is no reason to believe that the experimental diets of the dogs were deficient in vitamin B_2 for they contained separated milk, yeast, meat and often wheat germ, all sources of this substance. On the other hand, sources of vitamin A or carotene prevented the nervous degenerations completely, so that it seems probable that pellagra is due to a double deficiency in the food—the skin changes resulting from a B_2 deficiency and the nervous changes from an A deficiency. The experimental results described above in which the effect of yellow and white maize were compared, confirm the suggestion that a deficiency of vitamin A and carotene is the cause of the nervous changes in pellagra. Yellow maize containing carotene did not allow the spinal changes to occur, but actually prevented such changes being produced even by ergot. When white maize formed the cereal basis of the diet the nerve degeneration appeared (see p. 272). Again, the geographic distribution of pellagra in man seems to be in accord with these results. In America, and especially in the Southern States of the U.S.A. where pellagra is very prevalent, white maize or corn is generally eaten. In Java and the Dutch East Indies where yellow maize is eaten (although how extensively as compared with white maize I do not know), Jansen and Donath [30] report that pellagra is almost never seen. The above suggestions also receive support from observations published in 1928 by Underhill and Mendel [31] who described the effect of various substances, and especially of carotene (5 mg. daily), in curing black-tongue in dogs, a condition referred to above as being cured by the P-P factor of

Goldberger. Underhill and Mendel [31] confined their attention particularly to the mouth and alimentary canal and general condition of the experimental animals, and did not examine the nervous system. Incidentally, it is clear that the condition of "black tongue" as investigated by these various workers cannot be the same disease.

The final point as regards the ætiology of pellagra requiring consideration is whether maize or other cereals play an active part in the development of the disease owing to the presence in it of a toxic factor. Some of the experimental results above described suggest such to be the case. If this is true, then the embryo of the maize is probably richer in this toxic substance than the endosperm. I attempted to test this point experimentally but the results were too indefinite to allow any conclusions to be drawn.

To sum up, the evidence suggests strongly that a deficiency of vitamin A or carotene is the deciding factor in the development of nervous degenerative changes in pellagra. Deficiency of the pellagra-preventing factor seems to be responsible for the skin changes and there is a possibility that a toxic element in maize and other cereals, which is ineffective in the presence of sufficient vitamins A and B_2, must receive consideration. It seems probable that pellagra can be completely prevented and cured by the inclusion in the diet of green vegetables, carrots, milk, butter, egg yolk and mammalian liver. It is possible that, when the condition is very severe, the alimentary disorder may prevent the absorption of these foodstuffs and, if so, it will be necessary to inject carotene or concentrated vitamin A preparations intravenously.

Lathyrism.—Lathyrism, so extensively seen in India, is a disease of which I have no direct knowledge, but the clinical and pathological descriptions and history suggest that the experimental work on dogs may also throw some light on its ætiology and treatment. Clinical descriptions of lathyrism and the dietetic conditions under which it develops have been published by Stockman [32] and Acton [33] and others. The main facts appear to be that it develops in people : (1) who eat largely of lathyrus sativus peas ; and (2) in times of famine and drought when their diet is largely restricted to these peas.

There is still some doubt as to the causal agent of lathyrism. For instance, Anderson, Howard and Simonsen [34] found that the seeds of khesari (*Lathyrus sativus* L.) were harmless to ducks and monkeys, whereas akta (*Vicia sativa* L. var. *angustifolia*) produced symptoms in pigeons, ducks and monkeys. Attempts have been made by Stockman

[35], Dilling [36] and Acton and Chopra [37] among others to isolate a toxic agent from lathyrus peas. Stockman [35] found an alkaloid in small quantities which he thought might be responsible for the condition; Acton and Chopra [37] found an amine, and Anderson, Howard and Simonsen [34] thought that the base divicine found in akta might be the toxic agent. Dilling [36] isolated two alkaloids in very small quantities which caused increased spinal reflexes followed by paralysis in frogs, and weakness and paresis of the hind limbs of mice. Acton and Chopra [37] state that the toxic factor can be removed from the peas by soaking them in water.

Experimental work on animals with the object of producing lathyrism has never been very satisfactory. In no case, so far as I know, has good evidence been adduced that the weakness and spasticity produced in animals by diets containing lathyrus peas or by injecting chemical preparations made from these peas are associated with the degenerative cord changes seen in human lathyrism. Many of the experimental diets used by workers have been so defective that it would be surprising if the animals had not developed severe illness independently of the specific signs and symptoms of lathyrism. With the knowledge now at hand it ought to be simple to produce in experimental animals the spinal cord degeneration found in human lathyrism if the diets are more complete than those previously used by investigators and yet deficient in vitamin A and carotene. I have not yet been able to investigate this problem owing to the difficulty of getting a supply of the peas, but in a casual experiment I was interested to find characteristic cord changes in one animal whose diet consisted of beans 30 to 150 grm., separated milk powder 20 grm., meat 10 grm., yeast 5 grm., orange juice 3 c.c., sodium chloride 1 grm. (see Exp. XIV). Whether this result was due only to a deficiency of vitamin A, or to this deficiency acting in association with a toxic factor in the beans, cannot be stated. Another dog on a similar diet with the addition of cod-liver oil did not develop any degenerative changes in the spinal cord. The beans used in this experiment were dried haricot beans. Animals receiving dried peas did not, during the short period of the experiment, show any degenerative changes. I hope, however, to be able to investigate this problem in the near future.

It ought also to be an easy matter to see whether vitamin A or carotene has the specific curative and preventive effect in human lathyrism. As the result of a field study of lathyrism in India, Young advanced the suggestion that lathyrism is primarily a deficiency disease, and that vitamin A deficiency is the factor concerned. While the facts adduced by Young could be equally well used to support the possibility of other deficiencies being responsible for this disease—for instance, a deficiency of vitamin B_2—the experimental results above described are in support of Young's suggestion.

EXPERIMENT XIV.

Spinal Cord Degeneration in a Dog whose Diet included Dried Haricot Beans.

Age beginning: 10½ weeks.
Duration of experiment. About 3 months.
Basal diet: Separated milk powder, 20 grm.; lean meat, 20-10 grm.; peanut oil, 10 c.c.; orange juice, 3 c.c.; dried yeast, 2·5 grm.; salt, 2 grm.: irradiated ergosterol (vitamin D) 0·05-0·1 c.c.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Clinical notes
(*a*)	Dried beans	Degeneration in anterior, antero-lateral columns and direct cerebellar	Very quiet, gait not normal, but no very definite symptoms noticed
(*b*)	Dried beans Cod-liver oil	No degeneration	Normal

CORD CHANGES IN PERNICIOUS ANÆMIA.

Finally, the problem arises as to whether these experimental results have any relationship to the subacute combined degeneration of the cord associated with pernicious anæmia. It must be stated at once that the discussion on this point is largely hypothetical, and my own observations on this disease, although of an elementary nature, make it clear that the problem in this case is not so directly related to the animal results as are convulsive ergotism, lathyrism and pellagra. At the same time the demyelination of the cord fibres often found in pernicious anæmia is so characteristic a change that its production and prevention by the above described methods suggest that there may be a similar specific factor or factors involved in both the clinical and the experimental conditions. Nor is the exceptional nature of this pathological condition the only reason for suspecting some common factors in ætiology. Whatever the primary cause of pernicious anæmia may be, there seems little doubt that the liver is implicated in this disease since the administration of liver (Minot and Murphy [39]), by supplying a hormone (a compound containing β-hydroxyglutamic acid (West and Howe [40]) and ι-γ-hydroxyproline (Dakin, West and Howe [41]), brings about great improvement in the blood condition. There is, however, general agreement that watery extracts of liver, while they cure the blood condition over the period, do not stop the degeneration of the cord. Indeed, it is said that the nervous symptoms are often more severe to-day, since the liver treatment was introduced, than they were previously; for, whereas the blood condition is generally brought back to normal by liver extracts, and the life of the patient lengthened, the cord changes become progressively worse. Ungley and Suzman [42] have recently found that whereas the nervous symptoms often become worse during treatment with liver extracts, curative changes and general improvement both in the blood-picture and in the nervous condition result when whole liver is administered. If this is the case, it seems probable that the substance present in the whole liver, and absent from the extracts of the liver, acting in this way on the nervous system, is vitamin A. My own experience in connection with the cord changes of pernicious anæmia is very small. The nervous symptoms in one patient under my charge suffering from pernicious anæmia became definitely worse when ordered whole liver, and later, liver extract and cod-liver oil. Unfortunately, she was an out-patient during treatment, so that it is very difficult to make any deductions from this case. She was admitted to hospital later in a comatose condition, with a bacterial infection of the kidneys, and post mortem her liver contained only a small amount of vitamin A (79 blue units per gramme), although much more would have been expected in view of her suggested treatment.

It appeared to me at one time possible that the liver in pernicious anæmia could not store vitamin A in a normal way, but this cannot be always the case because in another patient suffering from pernicious anæmia who had died of a pyelo-nephritis the liver was found to be very rich in vitamin A (10,560 blue units per gramme of liver). This liver was kindly sent to me by Dr. Perdrau. It is possible, of course, that although the pernicious anæmia patient may be able to store vitamin A, there is sometimes a failure of an unknown nature which prevents this substance exerting its normal function on the central nervous system. An analogous instance suggesting the possibility of such an explanation is seen in diabetes mellitus, since, according to Pollak [43], the pancreas of patients deceased of this condition usually contains insulin in fair quantities, i.e., roughly half that of normal people.

The two main pathological conditions associated with pernicious anæmia, i.e., the blood changes and the cord changes, so often develop independently and react so differently to treatment that the idea that each is controlled by a separate chemical mechanism seems likely. It would certainly be interesting if both of these chemical failures could be associated with failure of one organ, viz., the liver. It is obvious, however, that the known facts of this problem are too few at present to allow anything more than surmise, but the hypothesis has sufficient support to warrant further investigation along these lines.

It is also clear that there is a possibility of a relationship between this experimental work and other clinical conditions associated with degenerative changes in the spinal cord. Subacute systemic lesions of the cord, regarded by Orr and Rows [5] as falling in the hæmatogenous category, are also found in Addison's disease and cancer cachexia, and it would be of interest if it were found that carotene and vitamin A prevented or influenced these changes. On the other hand, there are the degenerative cord changes found in tabes dorsalis and general paralysis and said by these same workers to arise from toxins ascending the peripheral nerves in the lymph stream, which must receive consideration from this new angle. Again, the well-known remissions seen in disseminated sclerosis suggest that there may be some protective mechanism of the nervous system such as is exerted by carotene and vitamin A, which at times comes into action and not only prevents extension but even, in the early stages at least, has a curative influence. It is evident that in this clinical condition also the protective effect of these substances is worth testing. It may be, of course, that the protective influence of carotene and vitamin A can only be exerted in the case of specific nerve toxins obtaining access to the nervous system in a particular way, for instance, via the blood-stream and not via the lymph. Or, it may be that they readily antagonize and prevent the changes associated with a high cereal diet and ergot but give no protection against the toxin of treponema pallidum or that producing disseminated sclerosis. At all events these points can be easily tested clinically.

It is true that so far as this experimental work is concerned pathological changes in the spinal cord have only arisen as the result of a gross deficiency of vitamin A or carotene in the diet. It is doubtful, however, whether under ordinary dietetic conditions a deficiency so intense is of common occurrence in this country. On the other hand, an insufficiency of vitamin A and carotene in the general diet of highly organized communities is undoubtedly very widespread. The question arises as to whether the partial deficiency of these protective substances is responsible for slighter, but possibly more frequently seen, abnormalities of the nervous system. For instance, the effect of deficiency in vitamin A intake in producing epithelial hyperplasia often associated with bacterial invasion suggests that this substance may have a similar influence on the development of nervous tissue. Women in pregnancy not only have to be provided with sufficient vitamin A to keep their own tissues working but must themselves pass on large quantities to the developing fœtus. Does the nervous system of the infant suffer when this supply is deficient? How such a partial deficiency of vitamin A or carotene might influence the human nervous system at different periods of life is not known. Anybody with experience of feeding young animals on experimental diets must be impressed by the difference in energy and activity among puppies brought up respectively on diets rich and poor in vitamin A. Similar differences in human dietary in early life may be of equal significance.

As regards the effect of gross deficiency of vitamin A described above, although all attention has been given to the spinal cord it must be added that the mental changes evidence by the general behaviour of the animals are also great and demand investigation. It is indeed clear that the functioning of the more highly developed parts of the brain is greatly influenced by dietetic constituents and the possibility that cerebral development and activity are to some extent retarded by dietetic defects short of those tested in this experimental work must be borne in mind.

One final point must be referred to. The anti-infective action of vitamin A and carotene is on a firm experimental basis. Clinically the uses and limitations of this action have not been worked out, but even so experience indicates that the phenomenon will undoubtedly prove to be of significance in the case of some human infections. The question presents itself, whether the protective effect of vitamin A and carotene against demyelination of nerve fibres and their anti-infective action against some kinds of bacterial infection may not have special significance in the case of the nervous system. Is it not possible, for instance, that the beneficial effect of the malarial treatment of general paralysis of the insane is due to the liberation of large quantities of vitamin A and other protective factors from the livers of patients infected with the malarial parasite? It might be worth while before giving malarial treatment in such patients to fill their liver up with this vitamin by giving diets rich in this substance and cod-liver oil. It is possible that the uncertainty of this strange form of treatment would disappear if this factor were taken into consideration.

The foregoing experimental work demonstrates that nutritional influences on the central nervous system, both in the sense of protective and harmful action, are sufficiently important to warrant their consideration in the clinical investigation of many pathological changes of the nervous system.

SUMMARY.

(1) When diets containing a large amount of cereal (other than yellow maize) and deficient in vitamin A or carotene are eaten by young puppies, degenerative changes in the spinal cord in the form of demyelination of the nerve fibres, which can be readily observed by Marchi's method of staining, can generally be observed.

(2) The addition to the diet of 2 to 5 grm. of ergot daily under these conditions hastens and intensifies these degenerative changes. Rye germ also hastens the changes and in some experiments wheat germ has been found to have a similar but less pronounced effect.

(3) The presence in the diet of any rich source of vitamin A such as liver oil (mammalian or fish), whole milk, butter or egg yolk or some source of carotene such as green vegetables or carrots, or carotene itself, prevents or diminishes these degenerative changes even when ergot is eaten.

(4) Spinal cord degeneration of this type does not seem to develop until the reserves of vitamin A in the liver are dispersed. Since these stores may be very large in well-fed animals, the time of onset of the symptoms of spasticity, inco-ordination and weakness varies greatly in different litters of animals. In the case of ergot, the changes are seen usually after two to four months on the diet.

(5) Not only do vitamin A and carotene prevent the degenerative changes but even in affected animals, the improvement in the clinical condition on the addition of either of these substances to the diet is very great.

(6) The possible bearing of these results on convulsive ergotism, pellagra, lathyrism and the subacute combined degeneration in pernicious anæmia, tabes dorsalis, disseminateds clerosis and even on the malarial treatment of nervous syphilis is discussed.

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LESIONS OF THE CENTRAL NERVOUS SYSTEM CHARACTERISTIC OF PELLAGRA.

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THE autopsy was performed by Dr. William H. Snyder. The author wishes to express appreciation for his co-operation and aid in the study of the material.

INTRODUCTION.

Winkelman, in 1926, found 2,000 articles relating to the ætiology, clinical or pathological findings in pellagra. It is strange that with so much interest so little progress has been made in knowledge concerning this abnormality. Pellagra is commonly believed to be a deficiency disease; formerly it was considered to be due to eating spoiled maize, especially after this grain had been carried on an ocean voyage. Goldberger, in particular, has studied the relation of pellagra to food; Goldberger and Wheeler (1920) were able to produce symptoms of pellagra in white male convicts who submitted voluntarily to a restricted diet.

Clinically, the disease is characterized by four abnormalities; symmetrical skin lesions, sore tongue, diarrhœa and psychiatric or nervous manifestations. A history of restricted diet is usually obtained. An achylia gastrica is very often present; similar lack of free acid in the stomach is also present in other conditions associated with spinal cord damage, such as pernicious anæmia and carcinoma of the stomach. The relation of these different changes, one to the other, is not understood. The dermatologist might affirm, for example, that the primary abnormality was an increased sensitivity of the skin to light, so that lesions appeared on the exposed surfaces of the body. Toxins absorbed from the skin might then cause the irritation of the gastro-intestinal and central nervous systems. Or the neurologist might feel that the changes in the nervous system are primary, not only in the brain and spinal cord, but also in the autonomic cells scattered throughout the body. The injury of the autonomic cells would then be held responsible for the cutaneous and gastro-intestinal manifestations. Fascinating as it is to speculate in this way, there is no basis at the present time for such conjectures.

The lesions of the nervous system have been studied by many workers, and in order to understand the findings one fact must be borne in mind. The disease attacks the brain, cord and peripheral ganglia everywhere, so that the lesions are extremely diffuse. In most cases, however, one portion of the nervous system bears the brunt of the attack. If this is the cortex, the mental symptoms are most prominent; if the lateral and posterior tracts of the cord, the ataxia, paralysis and spasticity. For this reason all types of nervous and mental symptoms have been described, and all types of changes in the brain and cord. Individuals with pellagra often show marked remissions with accentuation of the disease during the spring months. The nervous and mental symptoms are not usually early developments, and are often absent during the first bout of diarrhœa and dermatitis.

All types of mental changes may be found in pellagra. Many of the early cases have symptoms typical of neurasthenia, and these individuals are often considered to have purely functional ailments. Melancholia with suicidal tendencies is very common, but excitements, stupor, mutism and delirium occur often. Epileptic attacks have frequently been observed; headaches may be extremely severe.

The neurological abnormalities also present great variations. There may be burning pain in the extremities with tenderness on palpation of the nerves. There often is a diminution of tactile, thermal and painful sensibility. The muscles show an increased response to excitation. Ataxia is often present in the legs and less frequently in the arms. There may be a positive Romberg's sign. Tremor occurs in the arms or legs, and is sometimes of the intention type. Dysphagia and dysarthria occur. The deep reflexes are frequently hyperactive and associated with extensor plantar responses, absent abdominal reflexes and clonus. Tremors and paralyses of the facial muscles have been described. The tongue may show a coarse tremor.

At autopsy the Italian pathologists have found changes in the meninges in practically all their cases. There is an opacity and thickening of the pia-arachnoid, usually diffuse but circumscribed in some of the cases. At times hæmorrhages or purulent exudates have been present in the arachnoid. There is sometimes œdema of the brain; marked atrophy of the cerebral convolutions has been noted.

Almost all workers agree that fatty and pigmentary changes may be observed in the small cerebral arterioles and capillaries, with hyalin deposits, particularly marked in the capillaries.

Fat or pigment deposits of an abnormal character are common in the autonomic and sensory ganglia, but are present to a less degree in the cord, brain-stem, and in the cerebral cortex. The pigmentary changes occur in the cells of both the anterior and posterior columns of the cord; they are of the nature of pigmentary atrophy and are the expression of profound nutritional changes occurring in nerve cells. The abnormal pigment is not found in the nerve cells alone in pellagra, but also occurs in the cells of the heart, liver and spleen. Indeed, it has been stated that deposits of pigment in cardiac muscle are greater in pellagra than in any other disease.

The pigmentary changes are by no means the only abnormalities found in nerve cells. Alterations in the neurofibrils have been demonstrated, which are more marked in the large motor cells. Often the nucleus of the cell is eccentric, lying at the very edge of the cytoplasm. The nucleus may be atrophied or invisible, and the nucleolus stains with difficulty in many of the injured cells. Moreover, there is a loss of chromophilic granules in the nerve cells involved by this process; the granules are lost first from the central portion of the cytoplasm and later from the periphery.

Nerve fibres are altered even in the peripheral nerves. Many investigators have observed areas where the myelin sheaths had degenerated and free fat could be demonstrated in nerve trunks and in the cauda equina. All of the fibres appear to show a thinning of the myelin sheath.

The central canal of the cord is often obliterated, and there is an irregular proliferation of the ependymal cells. This is not characteristic of pellagra, but is present in many chronic toxic or infectious processes involving the spinal cord.

Wilson (1914) found granules in the neurolemmal cells of peripheral nerves which were stained violet with thionin. He called them π-granules and believed that they were increased in pellagra. It is known that neurolemmal cells round up and divide actively when the nerve fibres are injured.

In the spinal cord the fibres of the lateral, and less often of the posterior, columns bear the brunt of the injury. In many cases there is a pseudo-systematized degeneration of the antero-lateral columns. The condition does not differ radically from that found in primary anæmias, the so-called combined scleroses, except that the nerve cells are injured in pellagra. The lateral columns usually show the greatest injury in the thoracic portion of the cord, the posterior columns in the upper thoracic and cervical segments.

The posterior column changes resemble closely those found in tabes. There is, however, a maximal involvement at a different level in the spinal cord, for the posterior column involvement in tabes is more marked in the lumbar rather than in the thoracic segments. In tabes the root fibres are injured at the point where they enter the cord, while in pellagra the injurious agent attacks the whole primary sensory neurone, including the distal and proximal processes and the prolongation of the latter in the posterior columns. In pellagra the lateral pyramidal and the spino-cerebellar tracts in the lateral columns are also injured.

The cells of the posterior horns of the spinal cord often look quite normal in pellagra. In several cases the cells of Clarke's column have shown evidence of degeneration. The motor cells of the anterior horns exhibit changes which are present not only in the somatic motor but also in the autonomic cells.

There is no marked glial proliferation, but the areas where loss of cells or fibres have occurred are healed by glial overgrowth. There are often myelin bodies present in the sections of the cord stained with hæmatoxylin and eosin. Fat stains show droplets of fat either free or engulfed in phagocytic cells.

Similar changes may be found in the region of the brain-stem and cortex. Some brains show marked loss of cells and glial overgrowth; the changes are said to be most marked in the supragranular pyramidal layers.

The changes in the nervous system, in summary, are diffuse and are supposed to be of toxic origin. All portions of the neurones are involved, but some groups of cells are more often injured than others. Although the loss of nerve fibres in the tracts of the cord is diffuse, it often follows a definite pattern. The psychotic states are due to injury of the cortical neurones.

There are a few pathological changes in other portions of the body that may be mentioned. A general atrophy of all the striated musculature may occur. Similar atrophy involves the heart musculature and may be even more marked than in any other conditions. This has been related by some to disease of the cardiac autonomic cells, producing pigmentation and atrophy of the heart. There may be an involvement of the sympathetic cells, related to symptoms in the gastro-intestinal tract. Frequent inequality of the pupils may be explained upon a similar basis.

The question has arisen concerning the frequent association of pellagra and tuberculosis. It is said that patients with pellagra are especially prone to develop tuberculosis, and particularly intestinal tuberculosis. This was true of three out of five cases in one series that was examined. A fourth case in this group showed healed lesions of the lung. In another group of fifteen cases, tuberculosis occurred nine times.

With this summary of previous work upon the subject, a case may be presented showing many clinical and pathological findings typical of pellagra. Particular stress will be placed upon the changes in the nervous system.

CASE HISTORY, CLINICAL AND PATHOLOGICAL FINDINGS.

The patient, L. S. (J.H.H., unit 33389), was a white woman, aged 22, who was admitted to the Johns Hopkins Hospital, October 2, 1930. Only a meagre story of the illness could be obtained. The family history is of no significance. She is said to have been quite healthy until the beginning of the present trouble.

For three years previous to the present illness she had worked in a mill in Harrisburg, Pennsylvania. During this time the patient lived in a boarding house and nothing is known of her diet there. She returned to her home in Illsburg, Pa., in the fall of 1928 and remained well for two months, Then, in December, she had an illness which was diagnosed as influenza. She was very ill for a week and afterwards had a sore mouth. This trouble continued, and a few days later the patient developed a severe diarrhœa with five to ten stools a day, which persisted till she was admitted to the hospital.

Soon after the onset of the diarrhœa she developed a wet dermatitis which began on the backs of her hands, later appeared on her elbows, and still later on her keees. This dermatitis alternately dried and became wet to the time of her admission.

In June, 1929, she went to a clinic in Harrisburg and was told to take yeast. She did this for a week but stopped because it made her nauseated.

She had no nervous or mental symptoms until six weeks before coming to Baltimore. Then she became very nervous and irritable and showed some defects of memory. There was also drowsiness. The onset of the cerebral symptoms was rather acute. The nausea, vomiting and diarrhœa remained the same as it had been for eighteen months.

There seemed to be no dietary deficiency at home except that she ate little red meat.

On admission to the wards her temperature was 99·4° F., pulse 90, respirations 24, and the blood-pressure 110/80.

The patient was a tall, red-haired, very emaciated young woman. There was great weakness and she was obviously very ill. She seemed to be suffering pain in the region of the angle of the jaw and pointed to this area with her finger. The patient was unable to make herself understood because of difficulty in articulation; she seemed to be conscious and to understand what was said to her. At times she was irrational.

The skin was pale and drawn. There was a dermatitis characterized by almost absolute symmetry. The lesions were yellowish-pink, rough, in some places cracked and scaly. Over both hands the skin was rough and over the knuckles bright pink. The dermatitis was further distributed; a small patch on the palmar surface of each wrist, over the olecranon on both elbows, about the external nares, on the point of the chin, on both knees in a crescent on either side of each patella, and over the feet and ankles in a boot-like distribution. Over the perineum and genitalia the skin was red and in areas excoriated, due possibly to soiling with fæces. There was a decubitus ulcer over the sacrum.

The tongue and buccal mucosæ were fiery red. Along the tongue margins and inside of cheeks were ulcers, covered with a grey film of exudate. The lingual papillæ were not atrophic.

The conjunctivæ were very pale. The pupils were equal, regular and responded to light and on accommodation; the extra-ocular movements were normally performed. The patient appeared to suffer from bright light. Ophthalmoscopic examination revealed no abnormalities.

The external auditory meatus was lined by very dry, scaly skin. Hearing was normal. The mucosa was infected and the teeth were extremely carious, The tonsils were moderately enlarged and covered by a thick, grey exudate. There was deep injection of the pharyngeal mucosa. The glands at the angles of the jaw and along the anterior border of the sterno-cleidomastoid muscle were large, firm, discrete and extremely tender.

The thorax was flat and there were deep hollows above and below the clavicles. The respiratory movements were somewhat laboured, shallow and showed occasional irregularities. The percussion note was normal over the whole chest. The breath sounds were rather harsh. A few moist râles were heard at the bases, posteriorly.

The heart was normal, but the first sound at the apex was rather rough and followed by a loud, blowing systolic murmur. The pulse was regular, of fair volume and quality. The vessel walls were not felt.

The abdomen was flat and showed fair muscle tone. There was no muscle spasm or rigidity. The liver, spleen and kidneys were not felt. There were no abnormal masses. No peristalsis or intestinal patterns could be seen. There was moderate tenderness in the left lower quadrant.

The patient seemed to suffer considerable pain. There was a thickness of speech that made it unintelligible. There was a constant tremor of the facial muscles and a coarse tremor of the hands. The deep reflexes in the arms were hyperactive and equal on the two sides. The knee- and ankle-jerks were extremely active and there was bilateral sustained ankle clonus. The plantar reflexes were flexor; the abdominal reflexes absent. There was no increased tonus in the extremities. Sensory examination was unsatisfactory.

The red blood-cells numbered four million; the hæmoglobin was 74 per cent. The white blood-count was 9,440 with a normal differential. The Wassermann reaction was negative. The non-protein nitrogen was 25 mg. per cent.

Examination of the stools revealed no blood and no parasites.

The presence of the symmetrical skin lesions, sore tongue, psychiatric and neurological abnormalities, combined with the diarrhœa, suggested that this was pellagra, although there was no history of dietary insufficiency.

The patient was placed on a 5,000 calories, liquid diet, rich in vitamins. She showed no response to treatment. Her condition grew gradually worse and she died six days after entering the hospital.

Autopsy.—The conditions found were as follows (Path. No. 11663).

On opening the abdomen a greatly enlarged stomach covered practically all the abdominal contents. The intestines were crowded low in the abdomen and pelvis; they seemed small and were of a greyish white colour. The spleen and liver appeared normal.

The surface of the left lung was covered with dense adhesions of a stringy, tough, elastic nature, which held it firmly to the chest wall, diaphragm and pericardial sac. The left lung was free from adhesions and the pleural and pericardial surfaces were smooth.

The heart was small and its surface was smooth; the valves seemed delicate, although the mitral was a little thickened along its margin.

Both lungs showed the effect of aspiration of gastric contents. The left lung presented a number of caseous nodules, scattered throughout both upper and lower lobes. The bronchus was lined with necrotic material, evidently the result of aspiration. The bronchial nodes were quite small. Throughout the lung the lesions gave the suggestion of being related closely to the lumen of the bronchus.

In the lesser curvature of the stomach there was an area about 3 cm. in diameter, quite near the cardiac orifice, which was smooth and white. On section, the mucosa was found to give place suddenly to a scar-like patch which suggested an old, healed ulcer. There were some rugged ulcers in the lower part of the ileum with induration of their wall. In the colon, just past the ileo-cæcal valve, there were a number of shallow, rather ragged ulcers.

The liver showed no marked abnormality. The kidneys looked normal with smooth surfaces and normal striations. The aorta was delicate and elastic with only a little fat deposit. The uterus was extremely small. The bone-marrow of the femur was aplastic.

The meninges of the spinal cord and brain seemed somewhat thickened. No lesions visible to the unaided eye were visible in sections of the brain and spinal cord.

Microscopic study reveals relatively few abnormalities outside of the nervous system.

Sections of skin from the lesions on the hand, ankle and thigh were studied. There was a thickening of the corium over all these areas but no marked exfoliation. A moderate lymphocytic infiltration of the deep layers was present. The stratum germinativum was intact and of normal appearance everywhere. Elastic tissue stains revealed no further abnormalities.

In the heart there were a few small hæmorrhages between the muscle bundles. All the muscle fibres presented slight atrophy but no increase in pigment was present.

Sections of the left lung revealed many small tubercles with giant cells. The bronchi were filled with homogeneous pink-staining material infiltrated with leucocytes. Sections of the right lung showed the same material in the bronchi and alveoli, and some necrosis of the lung tissue. No tubercles were found in the right lung. A left bronchial lymph node was necrotic and contained numerous tubercles with giant cells.

There were numerous tuberculous ulcers in the colon extending down into the submucosa.

The thyroid was normal, except that the collagen in the alveoli was somewhat shrunken.

Sections of the stomach, liver, pancreas, spleen, kidneys, adrenals and ovaries revealed no abnormalities.

Sections of nerve trunks and of the nerve roots in the cauda equina appeared normal in sections stained with hæmatoxylin or with thionin. The neurolemmal cells, however, in places looked more numerous and rounder than normal, and the pink π-granules, described by Wilson, could be seen in the cytoplasm of these cells in sections stained with thionin. Fat stains of the nerves showed many droplets of free fat scattered in small groups among the nerve fibres.

The pia-arachnoid of the spinal cord and brain was very little thickened. Frozen sections of the spinal cord, stained for fat, revealed considerable neutral fat in the lateral columns in the position of the spino-cerebellar and lateral pyramidal tracts. This fat was present as free droplets and also in phagocytic cells which were most common around the walls of the small blood-vessels (fig. 2). Similar phagocytic cells were grouped in the arachnoid. Sections stained by the Spielmeyer method for myelin sheaths confirmed the finding of destruction of fibres, inasmuch as there was a considerable decrease in the number of myelinated fibres in the lateral column (fig. 1). The picture as seen with this stain was rather characteristic, inasmuch as there was no complete destruction of tracts or groups of fibres, but a general thinning out and decrease in the numbers. No involvement of the posterior or anterior columns was present. The lesions in the lateral columns were most marked in the upper thoracic and cervical portions of the cord, but they could also be demonstrated in the lumbar and sacral segments.

There was a general increase in the amount of lipoid pigment in the cytoplasm of all the nerve cells. This was greatest in the cells of the autonomic and sensory ganglia (figs 3 to 5), and of smaller amount in the cells of the central nervous system. The large motor cells of the cord contained considerable pigment (fig. 7). In the sensory ganglia the smaller sensory cells showed the greatest accumulation of pigment (figs 3 to 5). This was collected in the centre of the cytoplasm and the nuclei of the cells were markedly displaced. In the motor cells the pigmentation was near the edge of the cytoplasm, often at the base of the principal dendrite.

Many nerve cells presented evidence of severe injury; this was also true of those in the autonomic and sensory ganglia. There was often marked chromatolysis and the nucleus was displaced, as has been described. Certain cells were in the final stages of disintegration. In the cord the cells of the dorsal nucleus of Clarke (fig. 6) were the most markedly abnormal; the nuclei had crenated margins and were placed at the edge of the cytoplasm, considerable pigment was present and the chromophilic granules were very few in number. The changes in Clarke's nuclei are particularly interesting, in that these cells give rise to a portion of the spino-cerebellar fibres.

The motor cells in the ventral columns of the cord were in general normal, except for a much greater pigmentation than is found in healthy young people The motor cells in the medulla were more severely damaged and many cells in the facial and vagus nuclei showed chromatolysis. This explains the facial tremors and dysarthria observed in the patient.

No visible abnormalities were observed in sections of the cerebral cortex that would account for the mental symptoms.

The blood-vessels of the nervous system appeared normal, and there was no thickening or hyalinization of the vessel walls which has been described in cases of pellagra.

Discussion.

The patient showed the typical clinical findings of pellagra. A history of dietary insufficiency was not obtained, but no really adequate story could be elicited. Post-mortem examination revealed tuberculosis of the lungs and tuberculous ulcers of the bowel. The question naturally arises as to whether all the abnormalities may be explained upon the basis of the tuberculosis. Is pellagra a definite entity or group of symptoms which may be produced by several ætiological agents? Certainly the relation of diet to the disease is not yet entirely clear, for the results of feeding experiments upon rats cannot be applied directly to human problems. The only real proof of pellagra as a deficiency disease rests on the experiments of Goldberger and Wheeler on white convicts. There is another aspect to this problem. In cases of severe diarrhœa the patient may not be able to extract adequate substances from the diet to maintain a proper metabolism, and the remaining abnormalities may follow. For these reasons the tuberculous infection of the bowel cannot be lightly dismissed. Although tuberculous ulcers have been found frequently in patients who were supposed to die of pellagra, this does not affect the underlying question.

It was unfortunate that the patient was so ill on entrance to the hospital that the neurological examination was necessarily inadequate. There was delirium, and speech was unintelligible. A coarse tremor was noticed in the hands and in the facial muscles. The knee- and ankle-jerks were increased and there was ankle clonus. The abdominal reflexes were absent. It is interesting that the findings at autopsy may be correlated with the involvement of the spino-cerebellar and pyramidal tracts.

The neurological symptoms had been present for only a few weeks, and the lesions in the lateral columns of the cord were comparatively fresh. Thus fat was found in droplets and included in phagocytic cells.

The accumulation of pigment in the nerve cells was much greater than one would expect in an individual of this age. The cells of the autonomic and sensory ganglia showed the most marked pigment changes. In the spinal ganglia the smaller cells contained huge accumulations of pigment in the central portions of the cytoplasm. Since the spino-cerebellar tracts were the most involved, it is suggested that these cells are the primary sensory neurones of the spino-cerebellar pathway. It is unfortunate that no sensory examination could be made in this case. The dorsal column cells of Clarke showed marked degeneration. However, most of the cells in the anterior and posterior horns of the cord looked quite normal. There was some increase in pigment in the large, somatic motor cells.

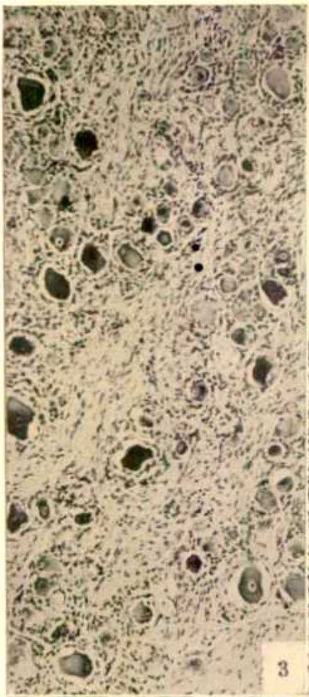
Two other pathological findings are worthy of note. The heart was extremely small and its fibres were atrophied. The uterus was also small and infantile. The small size of the heart in patients with pellagra has been frequently observed. It is probable that the small uterus is to be explained on the basis of the same underlying factor.

SUMMARY.

The patient, a white woman of 22, had symmetrical skin lesions, sore tongue, diarrhœa, mental and neurological symptoms characteristic of pellagra. There was no history of dietary insufficiency.

Histological study of the central nervous system revealed changes which have been considered typical of this disease. These abnormalities were extremely diffuse and involved all portions of the neurones. Accumulations of pigment were found in cells of the sensory and autonomic ganglia and those in the spinal cord and brain-stem. The antero-lateral columns of the cord were most severely

PLATE VII.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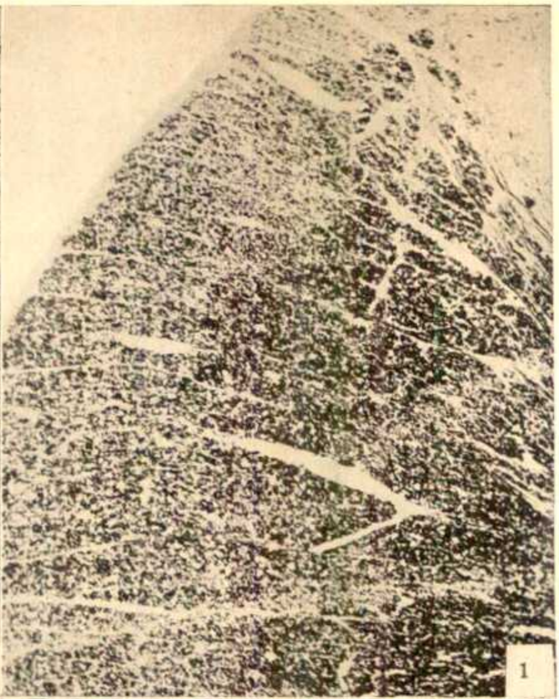
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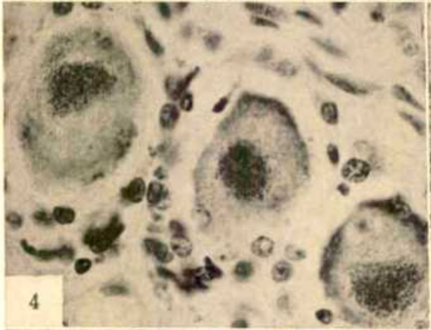
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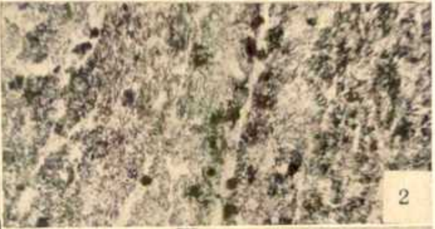
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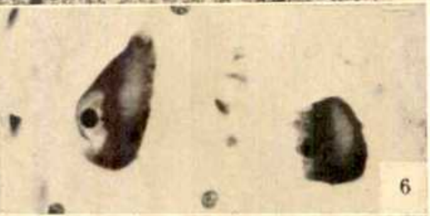
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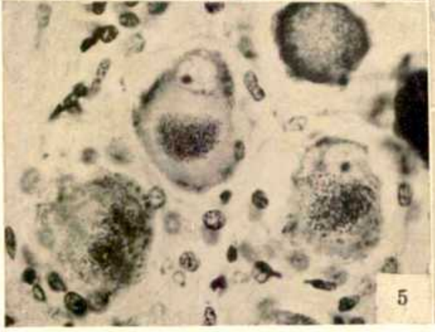
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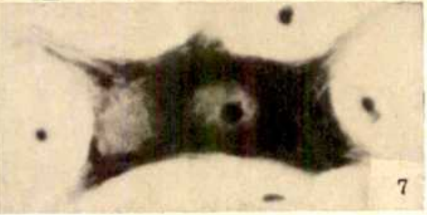
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To illustrate paper by Orthello R. Langworthy.

involved; there was no abnormality in the posterior columns. The lesions involved particularly the spino-cerebellar and cortico-spinal tracts. It is probable that the neurological abnormalities were of only short duration; considerable fat could be demonstrated in the lateral columns of the cord.

The small cells of the sensory ganglia showed the greatest deposit of pigment. It is suggested that these cells are the primary neurones of the spino-cerebellar pathway.

DESCRIPTION OF FIGURES.

PLATE VII.

FIG. 1.—Section of the spinal cord in the thoracic region stained by the Weigert-Pal method Only one lateral column is shown. It will be noticed that there is a distinct thinning of the number of medullated fibres at the edge of the cord in the region of the spino-cerebellar fibres and a smaller loss of fibres from the cortico-spinal tract.

FIG. 2—In the areas that showed a decrease of medullated fibres in fig 1 considerable fat could be demonstrated in frozen sections. Some of this fat was present as free droplets; the remainder was present in phagocytic cells which were particularly numerous around the small blood-vessels. This picture is in poor focus due to the thickness of the section. It does show fatty droplets and deeply staining phagocytic cells around the vessel wall.

FIG. 3.—Photomicrograph of the cells in a posterior root ganglion; the section was stained with thionin. The small cells in the upper centre show large collections of pigment in the central portion of the cytoplasm. Other cells show various stages of degeneration.

FIGS. 4 and 5.—High power photomicrographs of some of the smaller cells of a posterior root ganglion which show such marked pigment accumulations. The nuclei of two cells in fig. 5 are pushed to the edge of the cytoplasm The centre of the cytoplasm in all these cells is filled with a large mass of lipochrome pigment.

FIG. 6.—Degenerated cells of the dorsal nucleus of Clarke stained with thionin. The axones from these cells are spino-cerebellar fibres. Both nuclei are at the edge of the cells and the central portion of the cytoplasm contains pigment. The cell on the right appears to be disintegrating.

FIG. 7.—Less marked changes were found in the anterior horn cells of the spinal cord. There was an excess of pigment in the cytoplasm which is shown in this photomicrograph.

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THE EQUILIBRIUM BETWEEN CEREBROSPINAL FLUID AND BLOOD-PLASMA.

V.—THE OSMOTIC PRESSURE (FREEZING-POINT DEPRESSION) OF HUMAN CEREBROSPINAL FLUID AND BLOOD-SERUM.[1]

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MESTREZAT [1], 1912, determined depression of the freezing-point of the cerebrospinal fluid on five fasting normal subjects. These were patients who were about to be operated on under spinal anæsthesia, for hernia (three cases), varices (one case), and tumour of the leg (one case). The values obtained were − 0·57° C. in three cases, − 0·58° and − 0·59° C. in one case each. The value of the freezing-point of a mixture of twenty similar normal fluids was − 0·577° C.

Mestrezat did not make comparative determinations on the serum of these cases, but called attention to the fact that these values for cerebrospinal fluid are essentially the same as the average normal value for the freezing-point depression of the human serum. In the earlier literature, which was reviewed by Mestrezat [1], there is almost no reliable data on the freezing-point of normal cerebrospinal fluid, and none where it is compared directly to serum.

Depisch and Richter-Quittner [2] measured the freezing-point of cerebrospinal fluid and blood-serum in twenty-three patients. In only two of these cases was the spinal fluid normal. With one exception, Depisch and Richter-Quittner found the freezing-point depression of the spinal fluid greater than that of the serum. It is not stated whether these patients were fasting or not at the time the samples were obtained. They used the micro-method of Burian and Drucker [3], which may account for the discrepancy between their results and ours.

Teschler [4] is the only other author to give comparative data on the freezing-point of the cerebrospinal fluid and the serum in a series of cases. In a total of forty-three such determinations the freezing-point of the serum was the same as that of the cerebrospinal fluid within 0·005° in twenty cases. In the six "normal" cases only once did the freezing-points of serum and cerebrospinal fluid fail to agree within 0·005°.

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Teschler used a Beckmann thermometer. He does not state whether his patients were fasting or not. He concluded that the freezing-point of the cerebrospinal fluid is the same as that of the serum within the limits of error of the determination.

In this paper we report comparative freezing-point determinations on simultaneous samples of blood-serum and cerebrospinal fluid in ninety-four instances (on seventy-three patients).[1] These are shown in Tables I, II, III and IV. Twenty-three of these determinations on eight patients were in cases of various kinds of meningitis. Sixty-five of the non-meningitic cases and nine of the cases with meningitis were fasting nine hours, or more, before the samples of cerebrospinal fluid and blood were obtained.

The Beckmann apparatus was used exactly as described in Findlay's textbook [7], a Heidenhain thermometer being substituted for the Beckmann thermometer. Both serum and spinal fluid were collected under oil and kept on ice until the determinations were made. Determinations were started within half an hour of obtaining samples, that of spinal fluid usually being done first and the serum immediately afterwards. Three or more freezing-points were determined on each sample, the average figure for the three being given. In the vast majority of cases these three determinations did not vary more than 0·005°. The freezing-point of distilled water was determined at frequent intervals, usually on the day of each experiment. The temperature of the cooling bath was never more than 3° below the freezing-point. Super-cooling was kept at a minimum not exceeding half a degree. Seeding was done with a minute crystal of snow from that condensed on the sides of the glass jar containing the freezing mixture. Both the freezing mixture and the solution to be frozen were stirred by an electric device, at a uniform rate.

No stem correction was made. This error should be the same for serum and cerebrospinal fluid, as the room temperature rarely varied during the course of the determinations. No effort was made to correct for losses of carbon dioxide to the atmosphere after the samples were taken from under oil and placed in the freezing chamber.

Since the known errors in the method should be approximately the same for both serum and cerebrospinal fluid, we believe our data are significant for a comparison of the freezing-point of blood-serum with that of the cerebrospinal fluid.

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[1] Complete details of the examination of the blood-serum and spinal fluid in most of these cases may be found under the same case numbers in papers I and II of this series (V) and (VI).

RESULTS.

In forty-four of the seventy-one comparative determinations in non-meningitis cases, the freezing-point of the cerebrospinal fluid was the same as that of the serum within 0·005°. In only fifteen instances was the difference in freezing-point depression greater than 0·015°, the greatest difference being 0·037° (Case 220).

This indicates that the human cerebrospinal fluid is ordinarily in osmotic equilibrium with the blood-serum, and confirms the views of Mestrezat and Teschler. Occasionally, however, appreciable differences in freezing-point depression of these two fluids may occur. This is probably to be explained by the latent period before changes in composition of the blood are reflected in the lumbar cerebrospinal fluid. Ventricular fluid might be expected to reflect such changes with much greater rapidity.

Even in the cases of acute purulent and tuberculous meningitis (Table IV) where one would expect fever, sweating and vomiting to produce rapid changes in the composition of the blood, six of our twenty-three comparative determinations showed identical freezing-points within 0·005° C. while in only ten instances was the freezing-point difference between blood-serum and cerebrospinal fluid greater than 0·025° C. In each of these ten instances, moreover, the blood-serum was hypertonic to the spinal fluid, which is what one would expect if the patient were being rapidly dehydrated by sweating and vomiting and the spinal fluid had not reached equilibrium with the concentrated blood.

The spinal fluid in these cases of meningitis showed a distinct tendency to have a lower osmotic pressure than normal. In fifteen instances the freezing-point depression was less than 0·545° C. while in only four instances was it greater than 0·570° C. This tendency had been previously noted by Mestrezat [1]. The blood-serum was much more variable, in six instances having an osmotic pressure below normal, and in ten instances an osmotic pressure above normal. The extremely high serum value in Case 338 we are unable to explain. As the chlorides, non-protein nitrogen, and sugar on the same sample of serum were within normal limits the figure may be in error.

As we have pointed out previously [8, 9, 10] both serum and spinal fluid chlorides fall rapidly at the onset of meningitis as they do also in all acute febrile diseases. We believe this is the cause of the low osmotic pressure of the spinal fluid in meningitis. Whether this hypotonicity is still present in the blood at the time of lumbar puncture probably depends upon the degree of subsequent dehydration.

We have previously reported [11, 12, 13], that whereas water drinking is normally followed by only minor changes in the composition of the blood-serum, when the water is taken during a rising temperature or during the anti-diuretic action of posterior pituitary lobe extract, an appreciable dilution of the blood-serum takes place and this dilution is reflected in the cerebrospinal fluid. Table V shows this effect during typhoid vaccine fever (five cases), and Table VI during the anti-diuretic action of posterior pituitary extract (" vasopressin "[1]) (nine cases). The " vasopressin " was given by subcutaneous injection.

It will be seen in these cases that such experimentally induced dilution of the blood-serum is reflected in the cerebrospinal fluid and that these two fluids tend to remain in osmotic equilibrium.

DISCUSSION.

In two previous communications [14, 15], one of us (F.-S.) has reviewed the literature and has discussed the nature of the cerebrospinal fluid and the basis for considering it a dialysate in osmotic and hydrostatic equilibrium with the blood plasma. Thus it has been shown that the cerebrospinal fluid pressure may be varied at will either by varying the intracranial venous pressure [16] or by varying the osmotic pressure of the blood [17]. That the cerebrospinal fluid is formed largely from the choroid plexus is established both by the experiments of Dandy [18] and by the direct observations of Schaltenbrand and Putnam [19]. Moreover, Foley was able to reverse the flow of cerebrospinal fluid through the choroid plexus [20] and this one of us (F.-S.) has confirmed [21].

It remained to show that the cerebrospinal fluid had the same total osmotic pressure as the blood plasma, and to demonstrate that experimentally induced changes in the latter are reflected in the former. These results we are now reporting.

Such accumulative evidence from various angles leaves little room for doubt that the cerebrospinal fluid is a dialysate in equilibrium with the blood plasma.

SUMMARY.

In seventy-one comparative determinations of freezing-point depression of human blood-serum and cerebrospinal fluid in non-meningitic cases, the results were identical within the error of the method in over

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[1] Courtesy of Parke, Davis Company.

60 per cent. of the cases. In 80 per cent. the difference in freezing-point depression was less than 0·016° C.

Experimentally induced dilution of the blood-serum by water drinking during a rising fever or during the anti-diuretic action of posterior pituitary lobe extract is reflected by a similar dilution in the cerebrospinal fluid.

CONCLUSION.

The cerebrospinal fluid is a dialysate in osmotic equilibrium with the blood plasma.

TABLE I.—CASES WITH NORMAL CEREBROSPINAL FLUID.

Case No.	Freezing-point –.° C. Serum	C.Sp Fl
1	0·577	0·573
2	0·549	0·548
3	0·580	0·577
4	0·568	0·567
5	0·559	0·559
6	0·556	0·558
7	0·570	0·568
8	0·580	0·578
9	0·588	0·586
10	0.582	0·581
11	0·566	0·565
12	0·576	0·578
23	0·549	0·551
24	0·557	0·559
25	0·589	0·589
26	0·550	0·549
27	0·560	0·555
28	0·542	0·541
38	0·565	0·567
46	0·583	0·561
48	0·538	0·559
50	0·572	0·584
51	0·593	0·576
52	0·588	0·563
56	0·583	0·575
57	0·543	0·550
79*	0·568	0·571
119	0·584	0·570
123	0·577	0·557
126	0·578	0·583
157	0·537	0·538
160	0·561	0·574
187	0·536	0·537
329*	0·581	0·558
336	0·559	0.558
High	0·593	0·589
Low	0·536	0·537
Average	0·567	0·565

* Patients fasting less than nine hours.

TABLE II.—CASES WITH SLIGHT ABNORMALITIES IN CEREBROSPINAL FLUID.

Case No.		Freezing-point –.° C.	
		Serum	C.Sp. Fl.
39	..	0·582	0·584
40	..	0·567	0·563
41	..	0·575	0·573
42	..	0·571	0·573
43	..	0·560	0·563
44	..	0·563	0·561
45	..	0·577	0·560
47	..	0·599	0·576
49	..	0·600	0·575
53	..	0·590	0·567
54	..	0·582	0·563
55	..	0·582	0·568
58	..	0·576	0·585
59	..	0·589	0·567
73	..	0·590	0·590
326	..	0·577	0·574
96*	..	0·557	0·558
121	..	0·535	0·538
219	..	0·534	0·534
220	..	0·608	0·571
222*	..	0·596	0·597
High	..	0·608	0·597
Low	..	0·534	0·534
Average	..	0·577	0·568

* Patients fasting less than nine hours.

TABLE III.—CASES WITH ABNORMAL CEREBROSPINAL FLUID.

Case No.		Freezing-point –.° C.	
		Serum	C.Sp. Fl.
74	..	0·583	0·575
75	..	0·567	0·580
76	..	0·538	0·540
77	..	0·598	0·603
78	..	0·579	0·579
115*	..	0·570	0·555
175	..	0·564	0·570
208*	..	0·548	0·539
215	..	0·538	0·561
325	..	0·578	0·583
340	..	0·604	0·575
341	..	0·563	0·566
342	..	0·552	0·551
343	..	0·636	0·633
344	..	0·570	0·572
High	..	0·636	0·633
Low	..	0·538	0·539
Average	..	0·573	0·572

* Patients fasting less than nine hours.

TABLE IV.—CASES WITH ACUTE PURULENT AND TUBERCULOUS MENINGITIS.

Acute Purulent Meningitis.

Case No.		Freezing-point −.° C. Serum	C.Sp Fl.
272	..	0·524	0·526
273	..	0·555	0·527
278*	..	0·616	0·607
279	..	0·576	0·580
280	..	0·576	0·583
288*	..	0·501	0·490
290	..	0·535	0·490
298*	..	0·546	0·540
300*	..	0·537	0·532
301*	..	0·570	0·541
302*	..	0·595	0·557
303*	..	0·629	0·542
304*	..	0·634	0·542
305*	..	0·577	0·577
306*	..	0·552	0·528
307*	..	0·580	0·541
308*	..	0·562	0·557
309*	..	0·567	0·547

Tuberculous Meningitis.

Case No.		Serum	C.Sp Fl.
233	..	0·590	0·546
337	..	0·512	0·507
338	..	0·726	0·510
339	..	0·561	0·518
265*	..	0·525	0·519
High	..	0·726	0·607
Low	..	0·501	0·490
Average	..	0·571	0·539

* Patients fasting less than nine hours.

TABLE V.—THE EFFECT OF WATER DRINKING DURING THE ANTI-DIURETIC ACTION OF TYPHOID VACCINE FEVER UPON THE FREEZING-POINT DEPRESSION OF THE BLOOD-SERUM AND THE CEREBROSPINAL FLUID.

Case No.	Time of first sample	Freezing-point depression (−.° C.)	Time of injection of typhoid vaccine	Dose (millions bacteria)	Water ingested in interval (c.c.)	Urine output (c.c.)	Time of second sample	Freezing-point depression (−.° C.)	Change in freezing-point ° C.
	A.M.		A.M.				P.M.		
11	Serum 9.50	0·566	1·48	250	200	?	8	0·560	— 0·006
	C.S.F. 10.41	0·564					8·55	0·560	— 0·004
23	Serum 10	0·549	11·35	50	360	?	3·40	0·541	— 0·008
	C.S.F. 11	0·551					4·05	0·544	— 0·007
24	Serum 10.30	0·557	10·45	50	1,200	?	4·07	0·543	— 0·014
	C.S.F. 11	0·559					4·40	0·552	— 0·007
28	Serum 10.10	0·542	11·53	200	1,320	325	4·44	0·531	— 0·011
	C.S.F. 11.10	0·541					5·12	0·533	— 0·008
57	Serum 9.51	0·543	11	125	1,450	?	4·20	0·531	— 0·012
	C.S.F. 10.35	0·550					4·51	0·542	— 0·008

TABLE VI.—THE EFFECT OF WATER DRINKING DURING THE ANTIDIURETIC ACTION OF POSTERIOR LOBE PITUITARY EXTRACT (VASOPRESSIN), UPON THE FREEZING-POINT DEPRESSION OF THE BLOOD-SERUM AND THE CEREBROSPINAL FLUID.

Case No.	Time of first sample	Freezing-point depression	Time of injection of vasopressin	Dosage (c c.)	Water ingested in interval (c c.)	Urine output (c.c.)	Time of second sample	Freezing-point depression	Change in freezing-point ° C.
	A.M		A M.				P.M.		
4	Serum 10.20	0·568	11.45	0·50	1,800	300	3.07	0·543	— 0·025
	C.S.F. 11.10	0·567					2.50	0·570	+ 0·003
75	Serum 9.40	0·567	10.06	0·50	2,000	270	3	0·549	— 0·018
	C.S.F. 10	0·580					2.50	0·553	— 0·027
53	Serum 9.55	0·590	10.45	0·50	2,200	0	2	0·565	— 0·025
	C.S.F. 10.30	0·567					2	0·556	— 0·011
47	Serum 10	0·599	12.05	0·50	2,125	310	3.20	0·581	— 0·018
	C.S.F. 10.20	0·576					3.25	0·577	+ 0·001
41	Serum 12.07	0·575	12.09	0·25	3,000	235	3.23	0·541	— 0·034
	C.S.F. 12.17	0·573					3.25	0·561	— 0·012
126	Serum 9.32	0·578	10.35	0·50	3,350	0	2	0·541	— 0·037
	C.S.F. 10.30	0·583					1.45	0·565	— 0·018
78	Serum 9.30	0·579	11.15	0·50	3,350	450	3.13	0·520	— 0·059
	C.S.F. 11.05	0·579					3.30	0·528	— 0·051
119	Serum 9.55	0·584	11.15	0·50	3,685	522	2.50	0·553	— 0·031
	C.S.F. 10.40	0·570					2.46	0·558	— 0·012
59	Serum 9.55	0·589	10.55	0·50	4,020	680	3.45	0.542	— 0·047
	C.S.F. 10.53	0·567					3.20	0·541	— 0·026

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PARATHYROID TETANY IN DOGS, AND ITS ABOLITION BY CURARE.

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In the course of an investigation of the neurological mechanism concerned in the production of tetany, it was considered of importance to reconsider the effect of giving curare in this disease. That the poisonous action of curare is a peripheral one was established by the experiments of Claude Bernard [1] and Kolliker [2]. Evidence that the site of this action was a myoneural junction, and not the end-plate of the motor nerve, was first brought forward by Langley [3]. More recently, Lapicque [4] has considered the drug to produce a difference between the chronaxies of the motor nerve and of the muscle fibres by lengthening that of the latter. The action of curare in removing the muscle spasm of tetany has been recorded by various observers [5].

In our experiments, the thyroid—and their included parathyroid—glands were removed from a series of fourteen dogs, with resulting active tetany in twelve. Fits occurred in about two days after the operation, the limits being twenty-four and sixty-eight hours in this series.

APPEARANCE OF DOGS IN TETANY.

At the onset of the attack the dog appears to be in a shivering fit. It lies curled up, trembles and when disturbed will stand apathetically, with occasional clonic jerks or fibrillary tremors in various muscles of the body. Shortly afterwards, the animal lies upon its side, with outstretched legs and extended head. Increased tone in the muscles of the limbs is usually present from the first onset of the genuine spasms of tetany.

The latter consist of tonic, clonic and fibrillary muscular contractions. Though extensor tone is invariably increased, tonic fits are not always present. When they are, they are very striking. Uninterrupted rigidity occurs, and it is of such a degree that the limbs are flexed with great difficulty by the observer. The spasm may persist for hours unchanged. The limbs are chiefly affected, but some opisthotonus is frequently shown. The clonic convulsions may be superimposed upon some degree of tonic spasm ; often they are found alone. They consist of violent shock-like contractions of isolated muscles or groups of muscles, notably in the scalp, limbs and spinal muscles. Fibrillary twitches of small groups of muscle fibres are found coincident with the other elements of tetany, or as its sole manifestation.

ELECTRICAL REACTIONS.

Electrical reactions were taken by a simple technique [10] and were found to be a valuable and constant index of latent or active tetany. Increased excitability to galvanic stimulation occurred on the supervention of tetany, though the threshold varied considerably among normal dogs at different times, as the following table shows :—

VARIATIONS IN ELECTRICAL REACTIONS. (Highest and Lowest Record in 3 normal Dogs.)

Dog	1	2	3
K.C.C.	0·5-1·2 ma.	0·85-1·5 ma.	0·25 -0·85 ma.
K.O.C.	5·0-5·0	5·0 -7·5	1·2 -3·0
A.C.C.	1·8-2·2	2·2 -3·5	0·475-1·0
A.O.C.	1·4-2·2	1·2 -3·5	0·625-1·0

An example of the gross change on the onset of tetany is as :—

Dog 5	Normal	Tetany
K.C.C	1·2 ma.	0·28 ma.
K.O.C.	5·0, 7·5	0·7
A.C.C.	2·2	0·55
A.O.C.	1·6	0·17

With the exception of the kathode opening current (K.O.C.), the electrical reactions of one normal dog may be as low as, or lower than, those of another dog in tetany, though this is exceptional.

	Lowest normal (Dog 7)	Active tetany (Dog 6)
K.C.C.	0·25	0·4
K.O.C.	1·2	0·4
A.C.C.	0·43	0·8
A.O.C.	0·63	0·5

We obtained none of the grossly irregular and unpredictable relationships between the various forms of galvanic stimulus recorded by Paton and his co-workers [6]. Far the most constant and valuable indicator of electrical hyper-excitability, such as occurs in tetany, is the kathodal opening contraction (K.O.C.), and this is the criterion used in this paper. By K.O.C. is meant the minimal current in milliamperes which will excite a contraction of a muscle when the flow of the current is interrupted. In tetany K.O.C. is characteristically reduced to about one-tenth its normal value. In spite of the wide variations among normal dogs, we found no overlap between the readings of tetany and of normal excitability. A normal reading of under 1·0 ma. was quite exceptional in any dog, while a reading over 0·70 ma. was not found in any dog in active tetany. A reading of 0·5 ma. or under was a definite indication of tetany.

With regard to the other galvanic stimuli, we found the kathodal closing current (K.C.C.) threshold little worthy of reliance as a criterion of the form of excitability we were measuring. This is in agreement with the findings of Thiemich and Mann [8] in children. Von Pirquet [9] refers to anodal hyper-sensitivity being greater than kathodal in tetany, and this we confirmed. A.C.C. and A.O.C. frequently fell respectively to one-quarter and one-tenth normal.

Characteristic readings are:—

	Normal	Tetany
A.C.C. ..	1·62 ma. ..	0·68 ma.
A.O.C. ..	3·50 ..	0·37

We did not, however, find anodal readings as constant or reliable as kathodal. The order of sensitivity of the forms of stimulation is of little value as a criterion of hyper-sensitivity, with the possible exception of the frequent fall of A.O.C. below A.C.C. in tetany. Very occasionally A.O.C. was found to indicate latent tetany more readily than K.O.C., and for this reason the anodal reaction was always recorded.

THE ADMINISTRATION OF CURARE.

General observations.—The dogs used were of mixed breeds, most being mongrel spaniels or terriers of weights between 20 and 26 lb. Fourteen dogs were used in all. Curare was given to eight dogs in tetany and to six normal dogs. The curare—Messrs. Burroughs Wellcome's tablet preparation—was a resinous substance of somewhat poor solubility in warm saline, and it was not possible to ensure a constant rate of absorption when injected subcutaneously. Accurate dosage per kilogram of body-weight was not attempted, but the initial dose of 86·4 mg. was based upon a dose of 8·6 mg. per kilo approximating to that used by other workers. This dose killed the first dog in thirty-five minutes, having abolished violent tonic tetany of four hours' duration in twenty minutes; 54·0 mg. subsequently killed a normal dog in forty-five minutes.

Reduction of the dose abolished the spasm of tetany without consequent death or even obvious paralysis. Two examples will be quoted.

DOG 4.—SUMMARY.

Tetany followed thyroidectomy in twenty-four hours. The condition was one of tonic extensor rigidity of all four limbs, with superadded clonic contractions of the scalp and fibrillary tremors of limb and trunk muscles.

Tetany was observed continuously for twenty minutes. It was extremely severe and underwent no modifications. Curare (21·6 mg.) was then given subcutaneously, in one dose. The dog was unconscious.

Results.

In thirteen minutes the tonic spasm of the legs was much diminished.

In fifteen minutes the natural flaccidity of the limbs was restored, but clonic and fibrillary movements continued.

In twenty-five minutes there was complete cessation of clonic and fibrillary movements. The dog took notice.

Flaccidity remained for four hours, with the exception of slight rigidity at intervals after the first two hours.

Clonic and fibrillary twitches returned momentarily from time to time.

Voluntary movements of the limbs and head commenced at one hour after the abolition of the spasm, and within four hours the dog had leapt off the table and walked shakily across the floor.

DOG 5.—SUMMARY.

Tetany consisted throughout of clonic muscular spasms varying in degree from fibrillation of a few muscle fibres to shock-like contractions of large muscle groups. In the latter class the contractions appeared sometimes to be single, isochronous jerks of the muscle group at about one-second intervals.

At other times the jerk was made up of half a dozen or more very rapid isolated contractions, of the speed of a roll of a kettle-drum. Sometimes one massive group contraction was many times repeated (e.g., extension of the hind limb). At no time was tonic spasm or great spasticity observed. The walk was spastic and ataxic. In addition the limbs seemed weak. Laryngeal spasm was present.

Tetany was observed intermittently for one hour, and continuously for twenty minutes. Whilst varying in degree, it was never absent for more than a moment. Bouts of maximum severity were becoming more frequent and more severe, when the first dose of curare was given.

Curare (21·6 mg.) was given subcutaneously in two doses, separated by fifteen minutes interval. No diminution of tetany occurred between the doses.

Results.

In six minutes jerking of the limbs became very slight. Laryngeal spasm continued.

In ten minutes laryngeal spasm and tetany both vanished completely.

In fifteen minutes the dog walked, ran and wagged his tail. He seemed a little tired, but showed no signs of paresis.

In twenty-five minutes the electrical reactions still showed latent tetany.

In thirty-five minutes occasional twitches of one limb returned.

In fifty minutes clonic tetany and laryngismus were brought on by exercise. Both were relieved in two minutes by rest and oxygen inhalations.

DOSAGE OF CURARE.

In our first series of dogs in tetany, the results of giving curare were as under :—

Dog	Dose of curare	Tetany abolished in	Paralysis
2	86·4 mg.	15 mins.	Present (death 20 mins. later)
3	43·2 ,,	25 ,,	Present (death 55 mins. later)
4	21·6 ,,	25 ,,	Present (recovered)
5	21·7 ,, 10 8 ,,	25-35 ,,	Absent
6	27·0 ,,	25-35 ,,	,,
7	21·6 ,,	25-35 ,,	,,
8	27·0 ,,	25-35 ,,	,,
9	16·2 ,,	25-35 ,,	,,
10	27·0 ,,	25-35 ,,	,,

We then found a margin between the dose which would remove tetany and that required to produce paralysis.

Dog	Dose abolishing tetany	A dose which failed to produce paralysis
5	10·8 mg.	16·2 mg.
6	21·6 ,,	37·9 ,,
9	16·2 ,,	27·0 ,,
10	27·0 ,,	40·5 ,,

ELECTRICAL REACTIONS WITH PARATHORMONE AND CURARE.

In tetany abolished by parathormone, the electrical reactions rose coincidently with the removal of the spasm.

Dog	Normal K.O.C.	Tetany K.O.C.	Abolition of tetany by parathormone	
			Immediately (5-24 hrs.) K.O.C.	2-4 days K.O.C.
1	—	0·35 ma.	0·49 ma.	2·4 ma.
5	5·0	0·42	1·60	—
6	5·0	0·40	3·0	5·0
8	3·0	0·20	1·4	3 0
9	3·5	0·15	1·6	3·0
9	3·5	0·53	1·6	1·35

In tetany abolished by curare, there was no rise in electrical reactions unless the muscles were paralysed by a very large dose of the drug.

Dog	Normal K.O.C.	Tetany K.O.C.	Curare mg.	Abolition of tetany K.O.C.	Paralysis
9	4·0 ma.	0·15 ma.	40·5 ma.	0·40 ma.	Yes
12	5·0	0·50	54·0	1·70	,,
5	5·0	0·42	21·6	0·28	No
6	5·0	0·40	27·0	0·20	Slight weakness

Similarly with a normal dog, we found a rise in the electrical thresholds only when the muscles were paralysed by curare.

Dog	Normal K.O.C,	Curare mg.	Under curare K O.C.	Paralysis
17	2·9 ma.	48·6 ma.	4·1 ma.	Severe
15	4·5	48·6	5·5	,,
15	3·3	43·2	7·0	,,
11	6·0	32·4	5·0	Slight
11	6·0	40·5	8·0	,,
10	2·1	27·0	3·1	,,

In contradistinction to the above, high dosage with parathormone raises the electrical thresholds of the normal dog, sometimes to figures many times the normal. In one dog in which the normal K.O.C. was 1·2 ma. repeated increasing doses of parathormone raised this to 10·0 ma. This animal had 240 units of parathormone in 120 hours.

We found no rise in the serum calcium on giving curare either in doses adequate to remove tetany or in quantities producing profound paralysis.

A.—*Paralysis of normal dog.*

Dog	Normal	Curare paralysis
15	10·35 mg. per cent.	8·8 mg. per cent.
17	10·9 ,, ,,	10·8 ,, ,,

B.—*Relief of tetany.*

Dog	Normal	Tetany	Abolition of tetany by curare
9	10·5 mg. per cent.	6·8 mg. per cent.	6·7 mg. per cent.
10	11·2 ,, ,,	6·6 ,, ,,	5·0 ,, ,,

THEORETICAL CONSIDERATIONS.

There are a number of possible explanations of the phenomenon of the abolition of tetany by a dose of curare which does not paralyse the muscles affected, even temporarily.

(1) The action of the curare may represent a degree of myoneural paralysis only. The suddenness and completeness of the relief, combined with the margin between the antitetany and the paralytic dose of the drug, appears to us to render this explanation inacceptable.

(2) In the contractions of muscles produced by tetany, there may be a mechanism of selection of certain fibres. Curare may produce its effect by selective inhibition of the contraction of these same fibres.

In this connection must be mentioned the conclusion of Bremer and his co-workers, that curare acts selectively upon muscle fibres concerned with tone [7]. The abolition of clonic as well as of tonic convulsions suggests a selectivity of a wider nature.

(3) Curare may inhibit some link in an excitation reflex concerned in the production of tetany.

(4) Curare may have a central action upon some factor in the central nervous system which determines the distribution of the tetany contraction.

(5) The drug may act by a direct neutralization of a circulating toxin, the existence of which has repeatedly been postulated in parathyroid tetany.

SUMMARY.

(1) Curare abolishes active parathyroid tetany in dogs, constantly, rapidly and completely, but for a short time only.

(2) Much smaller doses of the drug are required to abolish tetany than those required to cause obvious paresis in either a normal dog or one in active or latent tetany.

(3) The action of curare, in small doses, or in any but those required to produce profound paralysis, is not accompanied by the rise of threshold to electrical stimulation, or by the rise in serum calcium which are constant accompaniments of tetany relieved by calcium or by parathyroid extract.

(4) Certain possible explanations of this action of curare in tetany are considered.

For the serum calcium estimations we are indebted to Dr. E. N. Allott. One of us (R. W.) was in receipt of a grant from the Royal Society, in aid of the above research.

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ON POSTURE AND POSTURAL REFLEX ACTION: THE EFFECT OF UNILATERAL LUMBAR SYMPATHETIC CHAIN EXTIRPATION.

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THIS monograph is an account of a series of observations made on the posture and postural reflex actions of decerebrate cats following removal of the ganglionated sympathetic chain in the lumbar region. The extensor muscles of the knee-joints (vasto-crurei) were selected as the postural muscles to be studied, and the changes in posture and postural reflex activity were examined in fifteen subjects.

These fifteen animals were divided into two groups. In the first group, consisting of eight cats, the left lumbar sympathetic chain was removed, the animals allowed to recover from the operation and then left undisturbed in cages for at least three weeks before decerebration was performed. In the second group, numbering seven cats, the left lumbar sympathetic chain was removed immediately after decerebration was performed.

The lumbar sympathetic chain was in each case extirpated from the level of the last thoracic ganglion to the brim of the pelvis through a mid-line incision in the anterior abdominal wall.

After decerebration, both vasto-crurei muscles in each cat were liberated from extraneous reflex effects by section of all the cutaneous nerves to both hind limbs, and tenotomy or motor-nerve section of all the other muscles in both hind limbs, thus leaving intact only the two vasto-crurei muscles and the branch of the femoral nerve supplying each of them. Each animal was then fixed on the operating table in the following manner. Holes were first drilled through the lower end of each femur and a rigid silver steel rod passed transversely through both holes. The cat was then placed supine on the table and the ends of the steel rod were clamped in two heavy upright cast-iron stands. The height of the steel rod was adjusted so that the caudal end of the cat's trunk was suspended and free from contact with the table. In order to guard against asymmetrical body stimuli, the shoulders were allowed to rest in a V-shaped wooden trough. The head was strapped in the mid-line with the neck in the fully-flexed position.

From the moment of mid-brain section at the operation of decerebration until the conclusion of all observations on each animal, artificia respiration was maintained by a stream of air which was blown into the cat's lungs at a rate varying between sixteen and twenty times a minute expiration being carried out in the intervals by passive collapse of the chest wall.

Anatomical controls were procured by photographing the extirpated sympathetic chains and the brain-stems removed from each animal at the conclusion of the observations. The integrity of the right lumbar sympathetic chain was investigated in each case by post-mortem examination.

OBSERVATIONS.

(1) *On posture.*—As the decerebrate cat recovered from the anæsthetic the limbs extended and the characteristic attitude of decerebrate rigidity developed.

All four limbs extended in both groups of cats, and if the animal were placed in the normal standing attitude it would remain standing and display no tendency to fall to one side or the other. On attempting to make the animal support the weight of the caudal end of the trunk on one hind leg alone, it became obvious that whereas the right leg would support the hindquarters in the normal posture and at approximately the normal height from the table level, the left leg (the left lumbar sympathetic chain having been removed) would not do this, and under the weight of the hindquarters gradually became flexed until the cat's trunk came to rest on the surface of the table. This phenomenon was constantly observed in both groups of decerebrate animals. With the cat fixed on the table in the manner described, the extensor rigidity was equally persistent in both hind limbs, lasting, in every case, for at least three hours. Flexion of tbe head caused increased extension of the hind limbs; extension of the head caused a decrease in the extension of the hind limbs; rotation of the head to one side or the other produced a reflex increase in the extension of the limb on the side to which the chin was rotated.

(2) *On postural reflex action.*

(*a*) *Lengthening and shortening reactions.*—On grasping the hind leg of an animal manifesting decerebrate rigidity and attempting to flex it, a considerable resistance is encountered. As the flexing force is increased the resistance suddenly disappears, and the knee-joint is carried easily and rapidly into a flexed position. If the leg be now released it will not return to its original extended position, but will remain approximately in the position to which it has been carried by the flexing force. The extensor muscle of the knee-joint has therefore taken up a new lengthened posture.

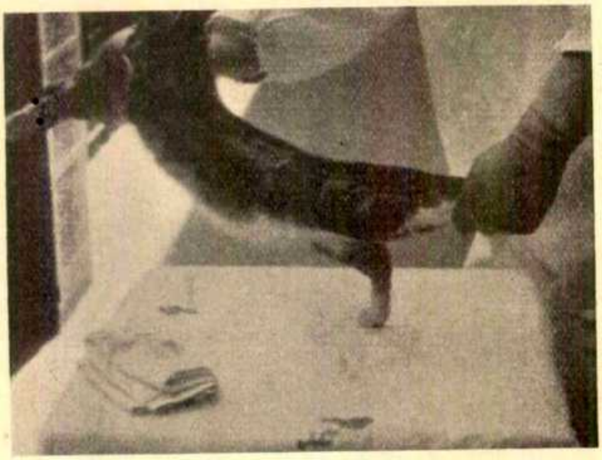

FIG. 1.—Cat No. 2. Caudal end of trunk is supported on the right hind leg. Decerebration and left lumbar sympathetic trunk extirpation performed one hour previously.

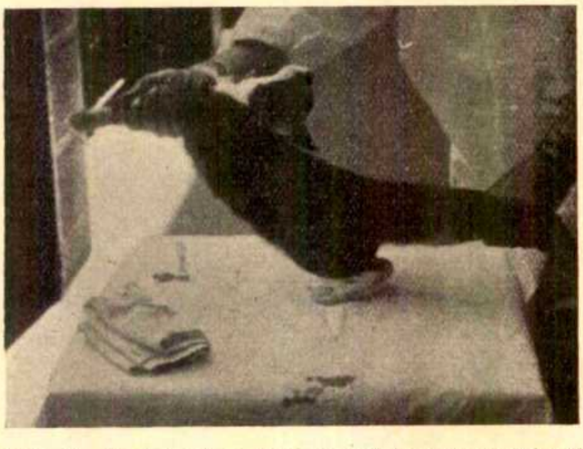

FIG. 2.—Cat No. 2. Caudal end of trunk cannot be supported by the left hind leg. Decerebration and left lumbar sympathetic trunk extirpation performed one hour previously.

Sherrington [1] has shown that this lengthening reaction is a reflex action subserved by a nervous arc, the afferent endings of which are proprioceptive in nature and are situated in the substance of the extensor muscle itself. The adequate stimulus for the excitation of the nerve endings is stretching of the muscle fibres among which they lie.

To elicit the shortening reaction the flexed knee-joint is passively extended, and on releasing the leg it is seen to remain in approximately the extended position to which it has been moved. Here the extensor muscle of the knee-joint has taken up a new shortened posture. This shortening reaction is a reflex action subserved by a nervous mechanism similar to that which mediates the lengthening reaction. In both groups of decerebrate cats lengthening and shortening reactions were constantly present in the vasto-crurei muscles of both sides. They could always be elicited by passive manipulation of the hind limbs.

On grasping the lower ends of the tibia simultaneously, one in each hand, with the animal in the fixed position on the table, and applying a gradually increasing flexing force, the characteristic resistance offered by the contraction of the vasto-crureus produced by the myotatic or stretch reflex was at first encountered in both limbs.

As the flexing force on each side was gradually and equally increased, the resistance offered by the left vasto-crureus was felt to yield under a flexing force which continued to produce a strong myotatic contraction on the right side; this flexing force thus produced a lengthening reaction on the left side and the left knee-joint was carried into a flexed position. As the flexing force was further increased on the right side, the myotatic contraction of the right vasto-crureus was finally overcome, the lengthening reaction was elicited and the right knee-joint carried into a flexed position.

This phenomenon was observed in every cat examined. When a load of 500 grams was suspended from the lower end of each tibia of a decerebrate cat in the fixed supine position, the left lumbar sympathetic trunk having been removed, the weight on the left side appeared to sink down gradually at an even rate until it came to rest upon the table; the weight on the right side, however, sank more gradually at first and, slowing down, came practically to rest some distance above the table, and finally sank slowly through the remaining distance to come to rest on the table.

The weight on the left side always appeared to reach the table from three to five seconds before that on the right side.

(*b*) *Crossed extensor reflexes.*—The crossed extensor reflex was first described by Philippson [2], and later more fully detailed by Sherrington. It consists in the reflex contraction of the lengthened vasto-crureus muscle of one side by the forceful passive extension of the opposite shortened tonic vasto-crureus. With the decerebrate cat in the fixed supine position manifesting rigidity in both hind limbs, the lengthening reaction was elicited in the left vasto-crureus by forceful passive flexion of the left knee-joint.

The posture now presented was extension of the right leg and flexion of the left. This asymmetrical posture of the hind limbs is the appropriate attitude for the examination of the crossed extensor reflexes. If the right leg be grasped and the tonic right vasto-crureus forcibly extended, a reflex contraction is produced in the left vasto-crureus and the left knee-joint takes up an extended posture.

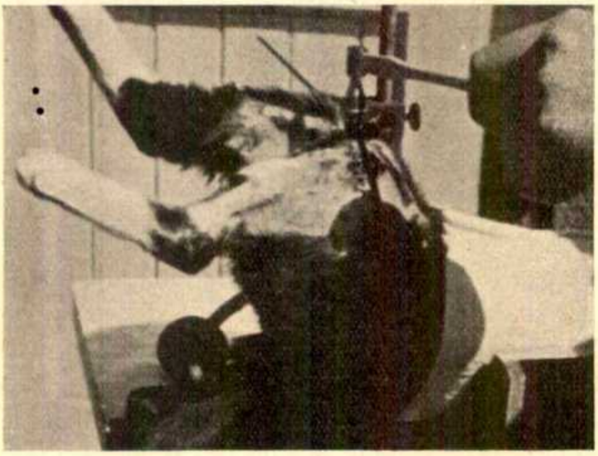

Fig. 3.—Cat No. 117. Decerebration two hours previously. Left lumbar sympathetic trunk removed twenty-one days previously. Posture of left hind leg after passive flexion of left knee-joint.

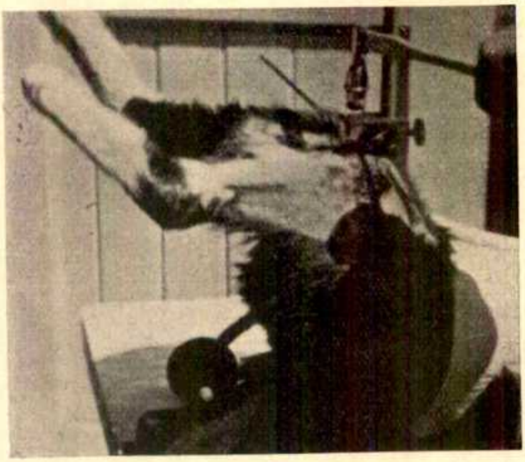

Fig. 4.—Increased extension of left knee-joint and alteration of posture produced by tapping the patellar tendon *once* with a percussion hammer.

This reflex contraction may now be produced on the right side by forceful passive extension of the tonic left vasto-crureus. These reflexes are subserved by nervous arcs, the afferent nerve endings of which are proprioceptive in nature and are situated in the substance of the vasto-crurei muscles. In both groups of decerebrate cats these reflexes were present in every case in both hind limbs. They were recorded myographically by attaching the lower ends of the animal's tibiæ to isotonic levers. It was observed, after removal of the left lumbar sympathetic chain, that the strength and amplitude of the motor response of the crossed extensor reflex was greater on the right side than on the left when an equal or a maximal amplitude of forcible passive extension was applied to the appropriate tonic muscle. It was also observed that the amplitude of passive extension required to produce a minimal motor response in the opposite muscle was always less on the left side.

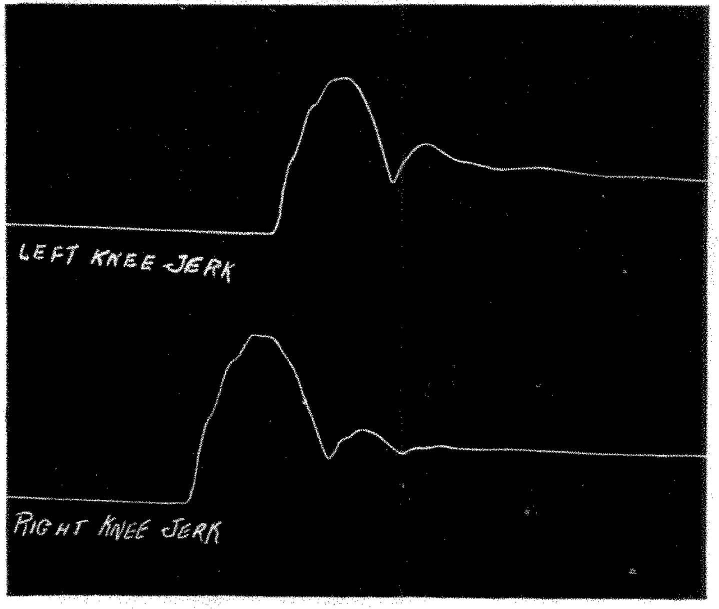

FIG. 5.—Records of knee-jerks of decerebrate cat, No. 10; decerebration performed three hours previously. Left lumbar sympathetic trunk removed at the same operation.

(c) *Knee-jerks.*—The knee-jerks were examined by inspection and myographic records made of them in both groups of decerebate cats. The jerks were elicited by tapping the patellar tendon with a small percussion hammer. If after passively flexing the knee-joint the patellar tendon were tapped several times with the percussion hammer, the joint presented a more extended posture after each tap until the original extended posture was finally regained (see figs. 3 and 4).

In recording the knee-jerks a lever system was used that was designed particularly to demonstrate the presence or absence of the myotatic or stretch reflex following the phasic response. This instrument consisted briefly of an isotonic lever, checked by a spring which prevented overthrow and maintained a slight persistent stretch on the postural muscle. A myogram of the knee-jerks is reproduced in fig. 5. In both groups of decerebrate cats the records of the knee-jerks showed that after the upward fling of the phasic response of the knee-jerk the extensor muscle on the left side (the left lumbar sympathetic chain having been removed) did not relax as far as the corresponding muscle on the opposite side, and that the left vasto-crureus came to rest at a shorter length than the right vasto-crureus, an observation that was made clear by the fact that the level of the tracing on the left side was higher following the knee-jerk than it was on the right side.

DISCUSSION.

It may be concluded from the preceding experiments that decerebrate rigidity develops and is maintained in the left hind limbs of decerebrate cats after removal of the left lumbar sympathetic chain. The postural reflexes exhibited by isolated postural muscle preparations are qualitatively unaltered by removal of the appropriate sympathetic nerve chain.

It must be concluded therefore that the post-ganglionic fibres of the sympathetic nervous system do not constitute the efferent limb of the reflex nervous arc subserving posture in skeletal muscle.

The positive changes in posture and postural reflex actions following removal of the left lumbar sympathetic chain in decerebrate cats may be summarized as follows:—

(1) The caudal end of the trunk can be supported at the normal standing height by the right leg but not by the left.

(2) A passive flexing force which on the left side is sufficiently great to elicit the lengthening reaction produces on the right side a myotatic contraction due to the stretch reflex. Further increase of this force on the right side elicits the lengthening reaction.

(3) The amplitude of the motor response of the crossed extensor reflex (Philippson's) is greater on the right side than on the left.

(4) The crossed extensor reflex may be produced on the right side by a smaller stimulus (less stretch) than is required for its production on the left side.

(5) The knee-jerk is followed by a myotatic contraction which on

the left side appears earlier during relaxation and is therefore produced by a smaller stimulus (less stretch) than the normal myotatic response on the right side.

Consider first the changes observed in the crossed extensor reflex. It has been noted that a smaller stimulus (less stretch) is required on the left side to produce a crossed reflex than is necessary on the right side. Left lumbar sympathetic chain removal could produce this effect in two ways.

(1) By increasing the excitability of the receptor nerve endings in the left vasto-crureus muscle; (2) by depressing the activity of the effector nerve endings in the left vasto-crureus muscle.

Consider these two possibilities in the light of the changes produced in the left knee-jerk by the same operative procedure. In this case after left lumbar sympathetic chain removal the left knee-jerk is followed by a postural (myotatic) contraction which appears earlier during relaxation than it does on the opposite normal side. Removal of the left lumbar sympathetic chain could also produce this change in two ways:—

(1) By increasing the excitability of the receptor nerve endings in the left vasto-crureus muscle; (2) by increasing the activity of the effector nerve endings in the same muscle.

From the consideration of these two postural reflex actions therefore, it seems probable that removal of the left lumbar sympathetic chain has increased the excitability of the proprioceptive nerve endings situated in the left vasto-crureus muscle.

When the lower end of the tibia of a decerebrate cat manifesting decerebrate rigidity is grasped and a gradually increasing flexing force is applied, the stretching of the postural muscles elicits in them a myotatic contraction through a proprioceptive reflex arc and a resistance is offered to the flexing force. As the force is increased, however, and the postural muscles are still further stretched, another type of proprioceptive nerve ending is stimulated at a certain threshold of tension in the muscle fibres. This new type of nerve ending inhibits the myotatic contract on and the leg may now be carried into a fully flexed position without any further increase in the flexing force. This lengthening reaction can be seen therefore to form, as it were, a background to the myotatic contraction. It only becomes obvious when the tension in the muscle fibres rises above a certain threshold value.

It can be seen therefore that if removal of the left lumbar sympathetic chain produces an increased excitability of the receptors in the left vasto-crureus muscle, not only will the myotatic contraction occur earlier when this muscle is stretched (which was noted to be the case following the knee-jerk), but also the threshold of tension necessary to elicit the lengthening reaction will be lower. This latter observation was seen to be true when two equal and gradually increasing flexing forces were applied to the hind limbs of a decerebrate cat after removal of the left lumbar sympathetic chain. The threshold of tension necessary to elicit the lengthening reaction was always arrived at more rapidly on the left side, and the left leg carried into flexion by a force which still continued to produce a myotatic contraction on the right side.

All the changes in posture and postural reflex activity that were observed to follow removal of the left lumbar sympathetic chain may be explained by the hypothesis that the effect of removing the sympathetic innervation to the vasto-crureus muscle was to increase the excitability of the receptor nerve endings situated within its substance. This hypothesis may throw some light on the functional significance of the fine non-medullated nerve fibres which have been noted to pass to muscle spindles and other proprioceptive end organs [3]. The origin of these fibres is still unknown, although Kulchitsky [4] believes that they are derived from the sympathetic nervous system. It is possible, however, that these fibres have some influence over the blood-supply or metabolism of the muscle spindles, and it is conceivable that their removal might readily disturb the excitability of those proprioceptive nerve endings subserving posture in skeletal muscle.

Whatever may be the explanation for the changes in posture and postural reflex activity in skeletal muscle following removal of its sympathetic innervation, nevertheless the author wishes to reiterate that skeletal muscle still exhibits postural tonus after removal of its sympathetic innervation. Postural contraction is not abolished by this procedure and reflex postural activity seems to be enhanced. All changes in postural tonus following sympathetic extirpation appear to be quantitative rather than qualitative in nature.

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I am deeply grateful to Professor C. W. Stump of Sydney for his advice and assistance during much of this work. The services of Mr. W. Jamieson of Sydney, as anæsthetist and assistant, were indispensable.

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TWO CASES OF OLIGODENDROGLIOMA:

WITH REMARKS ON THE GENERAL CLINICAL FEATURES OF SUCH CASES.

BY J. PURDON MARTIN.

INTRODUCTION.

THE tumours that have been called oligodendrogliomas form one of the better demarcated groups among the tumours that arise from cerebral tissues. Their histological picture is quite unlike that of any other cerebral growth. In their clinical features no absolute peculiarity has yet been recognized, but there is a certain constancy, and my primary object in this paper has been to review the clinical characters of my own cases and those previously recorded and see whether the clinical picture could not be made more precise. At the same time such deductions with regard to the life history of oligodendrogliomas as seemed legitimate from the clinical histories have been pointed out. In the account of my second case a larger pathological element has been introduced, because it seemed imperative to give a description of the very unusual features found after the patient's death.

In the two cases described in this paper the masses of tumour removed from the brain at operation were found on histological examination to consist almost entirely of small cells, of which the nuclei were easily stained, but the cytoplasm was indefinite and almost unstainable by any of the ordinary methods (figs. 2 and 6). Tumours showing this peculiar structure had been described by various writers before the recognition of oligodendroglia, and their origin had been attributed in one or two cases to the "third element" of Cajal. Bailey and Cushing [3] first suggested that these peculiar tumours arose from that fraction of the third element which had been named oligodendroglia, and they applied to them more or less tentatively the name "oligodendroglioma." In 1929 the subject was advanced further by the publication of an important paper by Bailey and Bucy [2]. These workers examined tumours of this type by the specific oligodendroglia stains of Hortega and of Penfield, and found that the cytoplasm of their cells stained deeply by these methods, and that it possessed elongated expansions similar to those of oligodendroglia. Some of the cells showed modifications in their form and in their staining reactions, which seemed to indicate that they were in stages of development or of degeneration, and there were many cells which seemed to be intermediate forms between oligodendroglia cells and astrocytes, but the conclusion was that these tumours were composed essentially of oligodendroglia.

The pathology of oligodendrogliomas has been fully dealt with by Bailey and Bucy, and no general discussion of it need be given here. For their recognition, recourse to the intricate specific staining methods for oligodendroglia is not necessary, because the histological picture obtained with ordinary stains is quite distinctive. In the accounts of the individual cases which follow instances of this picture will be described.

Oligodendrogliomas are rare tumours. Those described in this paper are the only ones that have been encountered at the National Hospital during the last ten years, and there is only one case recorded in the recent literature in this country. These facts, however, probably give an exaggerated idea of their rarity. Bailey and Cushing [3] found nine oligodendrogliomas among the 300 gliomatous tumours on which their monograph was based; Bailey and Bucy later described four others from the same clinic. Roussy, Lhermitte and Cornil [8] included a case in their study of the gliomas, and Schaffer [9] has also described one. Clinical accounts are given in four only of the cases recorded prior to Bailey and Bucy's paper [2]. Bailey and Bucy, including in their paper the cases previously referred to by Bailey and Cushing, gave full clinical records of four cases, and showed in a table some of the clinical features of nine other cases.

Case 1.—In September, 1929, Sir Percy Sargent operated on a patient of mine at the National Hospital, Queen Square, and removed from the left frontal lobe a mass of tumour which, on microscopical examination, was found to be an oligodendroglioma.

The patient, A. H., was a male, aged 38 at the time of operation. He had been employed as a railway worker for twenty-two years, and for five years had been an engine-driver, and was graded as a "First-class driver."

In the summer of 1925 he began to have occasional pain in the left half of the forehead, and on December 18, of the same year, he had a fit while asleep. After that he remained well except for occasional headaches until June, 1927, when he had a second fit. He then consulted a doctor and was put under treatment for epilepsy. During the next fifteen months he had no fits, but still had occasional frontal headaches, and "one or two turns of vomiting."

After the third convulsion, I examined him at the National Hospital, on October 3, 1928. The patient was quite normal mentally, and power, sensation and the reflexes were unaltered in all parts of the body. He was admitted to the hospital on November 26, 1928, and remained until December 19. Repeated clinical examination revealed no abnormality; the optic discs, though at first suspiciously red, were within the limits of the normal; the cerebrospinal fluid was normal and its pressure was not definitely raised (145 mm. of fluid).

In the X-ray films of the skull no abnormality was detected at that time, but the films, because of difficulty with the X-ray tubes, were not very good. On December 1 the patient had a group of three fits; these were generalized convulsions of sudden onset: the head and eyes turned forcibly to the right but otherwise the attacks presented no localizing features; no weakness or aphasia was observed after these attacks. In the next few days six more attacks occurred, all similar to those of the first group though less severe. At the end of June, 1929, I saw the patient again; he had not suffered even from a headache since his discharge from hospital and declared that he had never felt better in his life. He had been employed continuously since his discharge from hospital as a lamp-cleaner in the railway workshops. He remained free from obvious symptoms until the end of August, 1929. Then he had a severe bout of fits, followed by prolonged unconsciousness (lasting more than forty-eight hours) and was admitted in an unconscious state to the hospital at Peterborough. He was transferred to the National Hospital on September 6, 1929. Examination then showed bilateral choked disc but the functions of the cranial nerves were otherwise unaffected; power and sensation were normal in the limbs and there was no dysdiadochokinesis, but a fine tremor was present in the left hand; the abdominal reflexes were present but weaker on the right side than on the left; the tendon-jerks were equal on the two sides and the plantar reflexes were flexor as a rule, but the right was somewhat indefinite. He was taciturn and looked sullen, but he accepted all decisions without a murmur; he showed no defect in intelligence. The cerebrospinal fluid was normal, but its pressure was over 300 mm. of fluid and fell very little after the withdrawal of 5 c.c. of the fluid. Stereoscopic X-ray films showed an irregular stippled opacity in the left frontal region (Plate VIII, fig. 1); it lay close to the middle line and apparently towards the upper surface of the frontal lobe, spreading out in a position corresponding to the medial half of the superior surface of the lobe; the shadow did not appear to extend to the tip of the lobe either on the medial or superior surfaces. No change was seen in the bones of the skull. Re-examination of the films taken in November, 1928, now showed a blurred shadow of calcareous deposits in the same situation.

At the operation when the superior surface of the left frontal lobe was exposed, the tumour was seen at the anterior and upper corner of the bony opening. It was not attached to the dura. At first it seemed to be attached to the arachnoid, for when this was snipped through an edge of tumour could be raised from the surface of the brain. It was a dark bluish-red mass, slightly lobulated, and seemed at first to be overlying the brain. When its middle portion had been shrivelled by diathermy the peripheral part was gently raised from the brain and it was then found that the tumour extended deeply into the substance of the frontal lobe. A mass about the size of a small tangerine orange was removed, but the most anterior part of the tumour was not reached. Very little hæmorrhage resulted from the removal.

On the day following the operation the patient had a partial right hemiplegia and was completely aphasic, but he soon improved, and by the end of three weeks he was apparently completely well. He was given an intensive course of radium treatment and finally left hospital on December 4, 1929. At the time of his discharge the scalp flap in the operation area was not tense; the swelling of the optic discs had subsided without impairment of the visual acuity, and the functions of the other cranial nerves were normal; in the limbs the only abnormality was a fine tremor of the hands, definitely more pronounced in the left; there was no aphasia or apraxia; reading, writing and arithmetic were well performed and his memory was good; the only defect noticed in his mental functions was inability to describe spontaneously a sequence of events with which he was quite familiar, e.g., the path of the steam in the mechanism of a railway engine, though questioning showed that he understood the sequence. A small calcium-stippled mass was still shown in the brain by X-rays.

After histological examination of the mass removed at the operation, Dr. Greenfield reported: The specimen consists of several fairly large masses of tumour of a pinkish-red colour, which appear, to the naked eye, to be composed of a thick, fleshy outer part with a degenerated centre. *Histologically* the tumour is composed of masses of cells with small rounded nuclei and very indefinite cytoplasm. An indefinite matrix appears at the outer margin of the cytoplasm, but there is a circular zone of unstained or indefinitely granular material round the nucleus, which is limited by a faintly outlined cell capsule (Plate VIII, fig. 2, and Plate IX, fig. 3).

Blood-vessels of not much more than capillary diameter, but with thickish endothelial walls, are very numerous and rather regularly arranged, separating trabeculæ of tumour cells of about equal width. In the degenerated areas there are fairly thick bands of collagen representing the lines of the vessels but no nuclei are stained in these or in the intervening tissue. Between the degenerated portions and the more healthy tumour tissue are areas containing numerous, irregularly shaped, calcified knots, lying in a tissue which resembles dense neuroglia with fairly abundant trabeculæ.

The histological structure of the main mass of the tumour resembles closely oligodendroglia, and the tumour agrees well with the description of *oligodendroglioma.*

Progress after discharge.—The patient was seen in the out-patient department at intervals up till July, 1930, and was kept on luminal and bromide as a precautionary measure. At his first attendance he reported that he had had a fit; this was a mild, generalized convulsion which had begun with turning of the head and eyes to the right; after a few minutes he was quite well again. The scalp flap remained soft and the patient had no headaches. Intellectually and emotionally he seemed normal, and with the exception of a fine tremor of the left hand he presented no abnormal physical signs. He was still in this condition when he last attended (July 15, 1930), and for many months he had been working as an engine-driver in a restricted capacity. No further news of him was received until after his death. It appears that about the middle of October he began to show symptoms again. He became "dazed," and as he was making mistakes at his work he was discharged. His manner changed and he became indifferent. He then developed ptosis of his left eye and spasticity of his right leg, with an exaggerated knee-jerk, ankle clonus and a positive Babinski reflex. Later he became incontinent of urine and fæces and gradually became unconscious. He died on November 9, 1930. Throughout this last phase there were no local signs at the seat of operation.

The period of survival after operation was thirteen and a half months.

Comment on Case 1.—This case may be taken as a characteristic instance of oligodendroglioma. Typical features are: the age of the patient (35 to 38), the long history of symptoms, the absence of paralytic and the presence of "irritative" symptoms, the long remissions of symptoms, the presence in the tumour of calcareous deposits visible on the X-ray films and the fact that the tumour was situated in the frontal lobe. The primary result of the operation was excellent. The histological picture was characteristic, even to the presence of endothelial proliferation in the small blood-vessels. The scarcity of mitotic figures indicated the slowly growing nature of the tumour.

Case 2.—Two months after this first patient had been discharged from hospital, another case, which eventually proved to be one of oligodendroglioma, was admitted under the care of Dr. Hinds Howell.

E. C., male aged 43, a labourer. He complained of severe headaches of five weeks duration and of some unsteadiness in walking which had been present since an accident nine weeks previously. The patient showed a good deal of mental confusion. The history, obtained partly from the patient and partly from his daughter, was as follows: He had been healthy until three years before. Then he was knocked off his bicycle by a car and was unconscious for several minutes. There was, however, no indication of serious injury. After this he often complained of pain in the head, and there were periods in which he contradicted himself frequently in speech without realizing that he had done so. His headaches and confusion did not interfere with his work as a stoker. About a year before his admission he had complained very greatly of pain in his head and of "a film coming over his eyes." Nine weeks before admission he had a second accident; a bus in which he was travelling home from work collided with another vehicle and the patient was thrown against the seats and

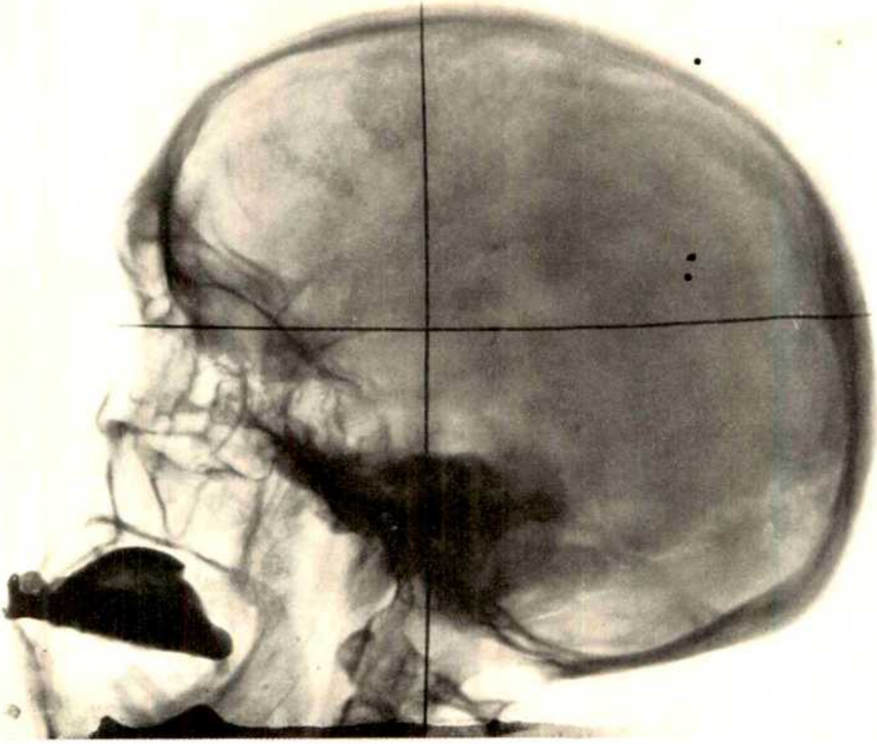


FIG. 1 (*Case* 1).—X-ray photograph of the patient's head, showing calcified deposits in the left frontal area.

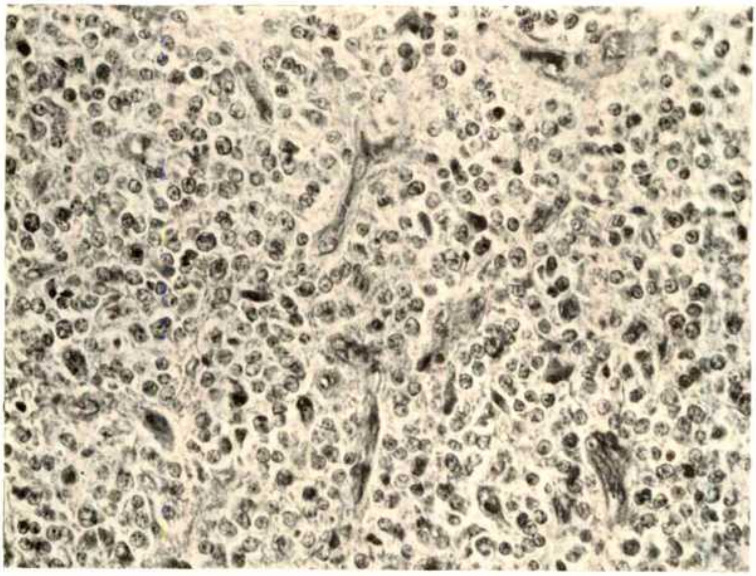


FIG. 2 (*Case* 1).—A section of the tumour. × 300. Hæmatoxylin and van Gieson. See the description in the text.

To illustrate paper by J. Purdon Martin.

PLATE IX.

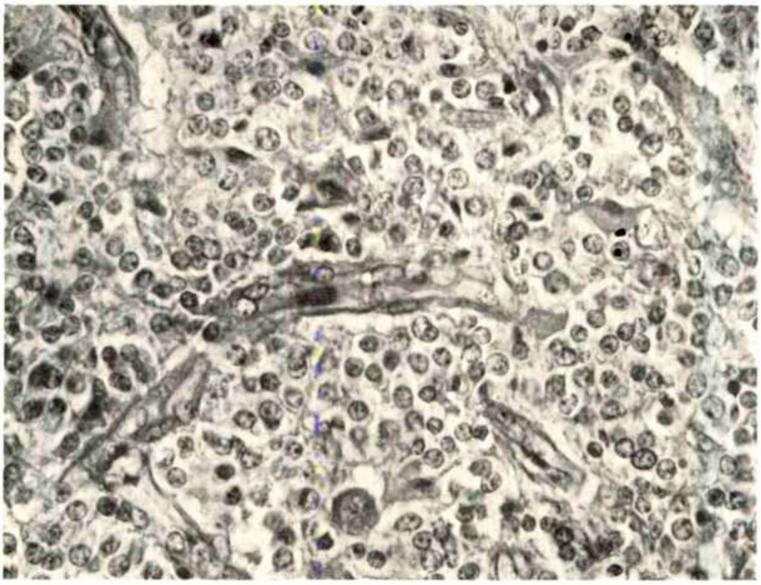


FIG. 3 (*Case* 1).—Another portion of the tumour. × 400. Same staining as in fig. 2. Nerve cells are present, though undergoing degeneration.

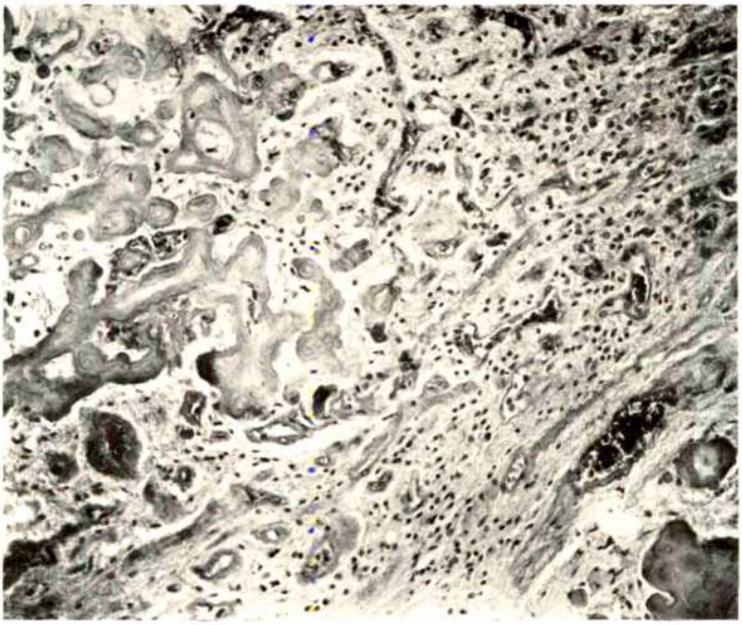


FIG. 4 (*Case* 1).—Another portion of the tumour after (incomplete) decalcification. The calcium deposits are primarily in the walls of blood-vessels.

To illustrate paper by J. Purdon Martin.

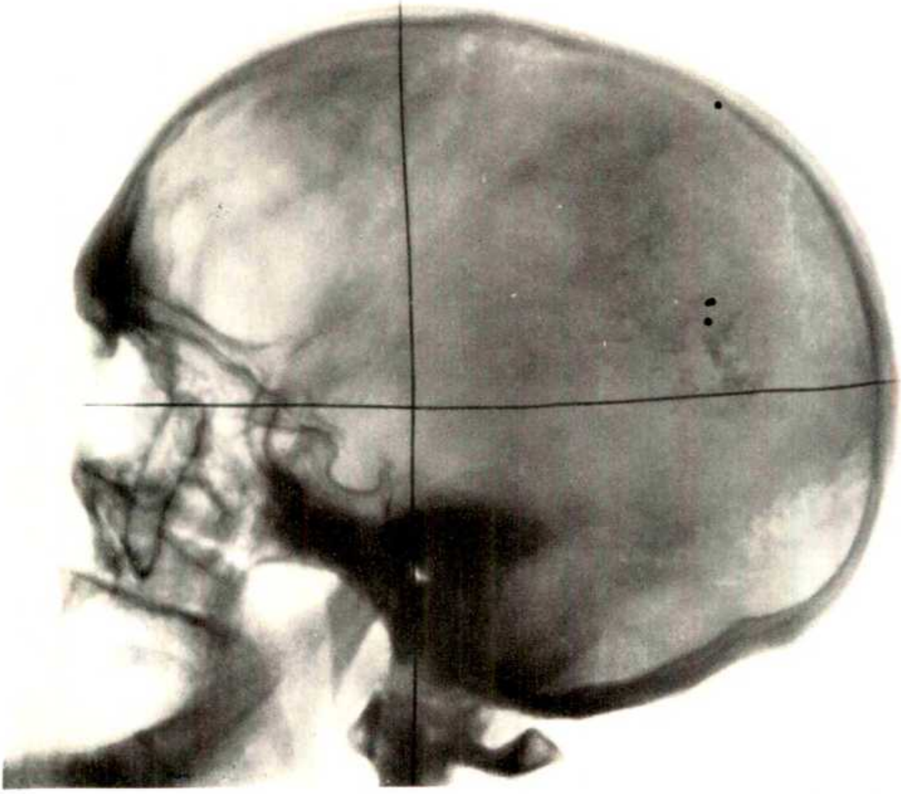


FIG. 5 (*Case* 2).—X-ray photograph of the patient's head, showing extensive calcification in the left parietal region.

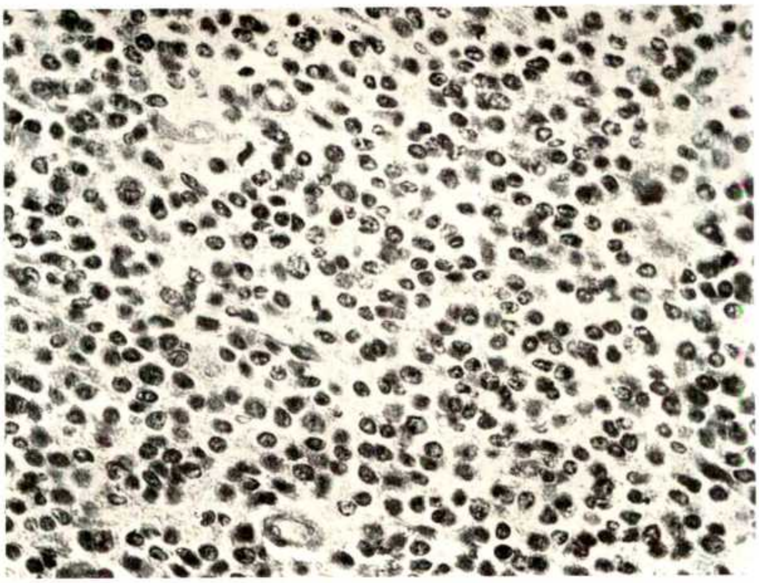


FIG. 6 (*Case* 2).—A section of the tumour. × 400. Hæmatoxylin and van Gieson. See the description in the text.

To illustrate paper by J. Purdon Martin.

PLATE XI.

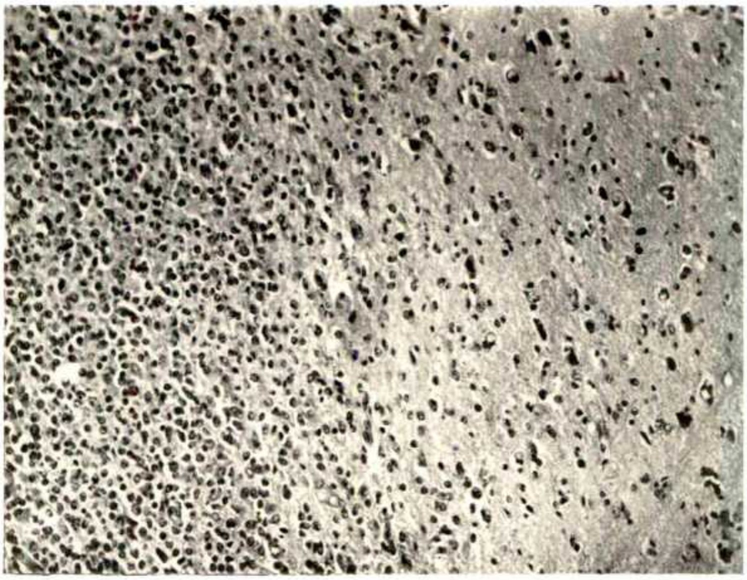


FIG. 7 (*Case* 2).—The edge of the tumour. × 150 (15 cm. represent 1 mm.). The transition from apparently healthy brain to tumour takes place over a space of about half a millimetre. From left to right in the figure the satellites of the nerve cells become rapidly more numerous. Same staining as fig. 6.

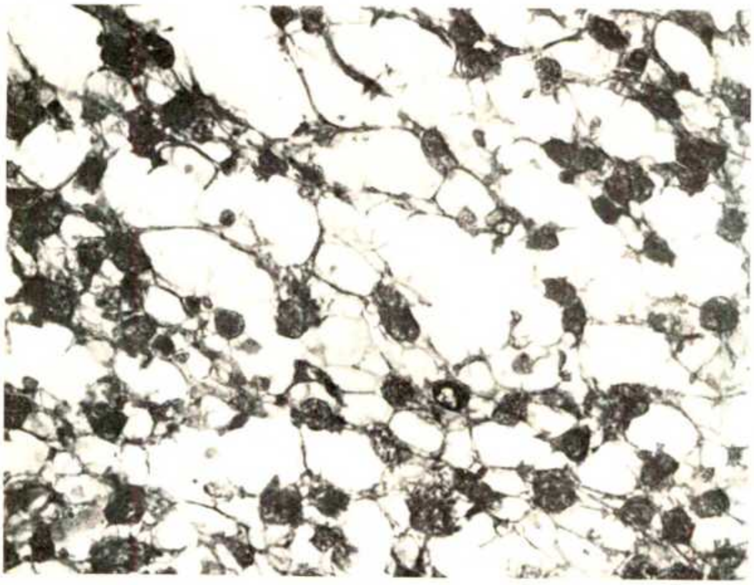


FIG. 8 (*Case* 2).—High-power view of a section of the tumour from the fourth ventricle. Mallory's stain. Note the apparent branching of the cells and the resulting network.

To illustrate paper by J. Purdon Martin.

his legs and back were bruised. He seems to have been definitely worse after this accident. He suffered from severe headaches, his sight became gradually worse, and he was unable to work. His right hand became unsteady and, in consequence, he was unable to write. He also had some unsteadiness in walking, and on several occasions he fell in the street. His memory became bad and he was mentally confused. He had never had any kind of fit and there had been no vomiting associated with his headaches.

Condition on admission.—The patient's intelligence was well below the average. Cerebration was slow. He was easily confused and his memory was poor. He presented no defect of speech and he made no mistakes in writing. Papillœdema was present in both eyes, the swelling amounting to about three dioptres in each. The visual acuity was, however, normal, and the visual fields were full. Some weakness was observed at the right angle of the mouth and the right eye could be opened against the patient's resistance rather more easily than the left. Otherwise the functions of the cranial nerves were normal. On the left half of the body no abnormal signs were detected. On the right side there was a slight tremor of the hand. Appreciation of passive movements of the fingers was not so good as on the left side, and discrimination of compass points was definitely worse on the right hand and forearm than on the left, but sensation was otherwise normal. The right abdominal reflexes were usually absent, and if present, tired easily. No weakness or inco-ordination of movement was found. The tendon-jerks were normal and the plantar reflexes flexor. The patient was more unsteady when standing on the right foot than when on the left, but his gait and usual stance were normal.

The alimentary, respiratory, and urinary systems were normal. The pressure of the cerebrospinal fluid was well over 300 mm. of fluid, and after the withdrawal of 5 c.c. of fluid it was still 280 mm. The fluid was slightly yellow, the total protein content amounted to 0·20 per cent. and the globulin tests were fairly strongly positive. The Lange curve did not rise above 2 in any tube. There were five cells per c.mm., all mononuclear. The Wassermann reaction was negative both in the cerebrospinal fluid and blood.

Stereoscopic X-rays of the skull showed little flecks and irregular streaks of calcification throughout a globular space in the left parietal region (Plate X, fig. 5).

The patient was operated on by Sir Percy Sargent on February 28, 1930. A large parietal bone flap having been turned down, some discoloration could be seen through the dura, and when the brain was exposed, a dark bluish-red tumour was found lying in the parietal lobe behind the post-central gyrus; the area of visible tumour was about the size of a two-shilling piece. With the aid of diathermy the tumour was demarcated and its more superficial parts separated from the brain substance; pieces forming altogether a mass as big as a hen's egg were then removed. There seemed to be a pedicle passing into the substance of the brain towards the corpus callosum. The tumour substance felt gritty. Radium needles were implanted in the tumour and the flap and wound were closed.

The patient made an excellent recovery and was discharged six weeks later.

The right arm when extended showed slight unsteadiness, but co-ordination in ordinary movements was good. There was no weakness of the limbs and the gait was good. Visual functions and speech were undisturbed.

Pathologist's report (*Dr. Greenfield*).—This is a very cellular tumour, composed of rounded or oval nuclei with very little cytoplasm between them (Plate X, fig. 6). What matrix is visible is indefinitely fibrillar and does not begin immediately round the nucleus, but in most places leaves a clear unstained circle round it. In some parts, there is, however, a more abundant matrix of a similar, ill-defined, fibrillar structure. Mitotic figures are very numerous. In some portions of the growth there is a considerable infiltration with connective tissue fibrils even between the tumour cells, and fine capillaries are abundant. The tumour has a fairly well defined margin in some places (Plate XI, fig. 7), but in others there is a transition from tumour to normal brain tissue through a wider zone of excessive cellularity. In one place numerous small gritty knots of calcification are present in the tumour.

The characteristics of the tumour approximate closely to those of the tumours described as *oligodendrogliomas.*

Progress after discharge.—This patient after his discharge from hospital remained relatively well for several months, but he suffered from headaches and was somewhat dull mentally, and consequently did not return to his work. After nine months he was re-admitted to the hospital. Ataxia of his right leg and astereognosis in his right hand were then definite and his speech was confused ; his cerebration was slow, he was drowsy and suffered much from headaches. There was a large cerebral hernia. Further operation was inadvisable and the patient died on February 9, 1930, eleven and a half months after his operation.

A post-mortem examination was performed by Dr. Greenfield fifteen hours after death.

When the scalp was being dissected anterior to the margin of the cerebral hernia, a small nodule, which appeared to be new growth, was found above and in front of the left ear. It was irregularly spherical and measured 1 cm. in diameter.

When the calvarium was removed the dura was found adherent in many places over the posterior half of the left cerebral hemisphere, but there was no invasion of it by new growth. Under it the tumour was visible occupying the medial half of the superior surface and the whole of the medial surface of the left parietal lobe. The outward appearance of the tumour, though mottled, was in most parts greyish and granular. Sections through the brain after fixation showed that the tumour was very large, occupying most of the parietal lobe and of the occipital lobe above the calcarine fissure. Medially, it invaded the splenium of the corpus callosum. It had invaded and largely filled the body and posterior horn of the left lateral ventricle. Below, the main mass of the growth involved the roof of the inferior horn in its posterior part. In the floor of this horn, right to its tip, there was an elongated extension from the tumour mass in the body of the ventricle. This extension was 3 or 4 mm. wide. It was pale, glistening and gelatinous-looking, just a little greyer (after fixation) than the white matter of the hemisphere. Along the floor of the anterior horn on this left side there was a thicker, wider and firmer deposit of similar glistening appearance.

In the third ventricle the anterior half was distended with growth of a mottled red colour, which invaded the walls of the infundibular portion and involved the optic chiasma. The posterior half of the third ventricle was thickly incrusted with growth similar in appearance to that in the horns of the left lateral ventricle.

In the right lateral ventricle there was an elongated, pale, glistening deposit along the floor of the anterior horn to its tip. This seemed to have a fine connection through the foramen of Munro with the mass in the third ventricle. On the floor of this right ventricle, at the junction of the posterior and inferior horns, there were two small masses of growth of the same pale gelatinous appearance. These were small circular bosses, each about 3 mm. in diameter. They were separate from each other and from all other growth. No growth was seen in the body of the right lateral ventricle or in its inferior horn. It could not be determined with the naked eye whether there was any extension of the growth from the third ventricle through the aqueduct of Sylvius, but the microscope showed that there were very delicate deposits on the ependyma of the aqueduct, and these were apparently continuous with the mass of growth in the third ventricle. In the fourth ventricle almost the whole of the floor was lightly frosted with growth of the same semi-transparent gelatinous appearance as in the horns of the lateral ventricles.

On microscopical examination the main mass of the growth showed the characters already found in the portion excised at operation. One feature that was more evident was that along small arteries the cells were arranged in rows, and broad prolongations of what was apparently cytoplasm extended down towards the vessel walls.

The pale gelatinous-looking masses in the floor of the ventricular horns and in the fourth ventricle were composed of very loosely formed tissue. (Fig. 8.) In celloidin sections stained with hæmatoxylin and Van Gieson's stain the nuclei, in places widely separated, almost seemed to lie free as in a smear. Faint shadows of unstained fibres could, however, be detected in the spaces between them as one moved the fine adjustment of the microscope and there were some portions of the tumours in which these fibres were lightly stained and could be seen clearly. The nuclei were of the same nature as in the main tumour, but they showed more variation in size and shape. Mitotic figures were very numerous. In paraffin sections stained in the same way the internuclear substance was more evident, but it stained indefinitely and it may be that to some extent the appearances seen in these sections were artefacts. In general, however, the appearances were confirmed by other sections. The cells appeared to possess branches and these branches joined and intertwined and the nuclei appeared as if caught in the net. In some places the nuclei were numerous and the amount of network relatively scant, while in other places, especially towards the base of each small tumour, the network was denser and the number of nuclei small. The branches in these sections appeared coarser than neuroglia fibres. Both paraffin and celloidin sections showed this network when stained with Mallory's connective tissue stain. In the looser parts of the tumour it took on a faint purplish colour, but where the growth was evidently older and firmer and the fibres formed a denser network their colour approached more closely to that taken by neuroglia fibres. In paraffin sections stained by Perdrau's method the network appeared to be formed by the union of prolongations of a granular cytoplasm which surrounded the nuclei; it did not take the silver stain at all intensely.

Cells departing from the general type were occasionally seen in all the sections and a few were large glial cells. Atypical cells were especially frequent in certain parts of the growth, e.g., in the tumour at the anterior end of the fourth ventricle. There giant cells were relatively numerous and the "transitional" forms illustrated by Bailey and Bucy [2] were to be recognized.

In these small masses of growth blood-vessels were numerous and they often had very thin walls. Along the more fully formed arterioles the tumour cells lay in dense rows, and on the side of each nucleus next the artery a mass of indefinitely stained cytoplasm extended towards the vessel. In the paraffin sections stained by Mallory's method a light purple stained fibre appeared to pass from this cytoplasmic mass on to the adventitia of the artery, and in at least one place these extensions on to the vessel seemed to have expanded feet. When the artery had been cut transversely by the section, the tumour cells were seen ranged in a rosette around it.

Where the incrustations on the ependymal surfaces were thick the brain tissue was invaded and there was an evident neuroglial reaction. But where the deposits were lightest, the ependyma under them was destroyed with little invasion of the sub-ependymal tissue; the growth had evidently been implanted on or skimmed along the ependyma:

The nodule which was found in the scalp showed an irregular mass of cells surrounded by dense fibrous tissue and divided by occasional incomplete fibrous septa. The cells had deeply staining nuclei and no appreciable cytoplasm in the hæmatoxylin and Van Gieson sections. They were massed most densely close to the fibrous septa. The nuclei were smaller and more deeply stained than in most parts of the cerebral growth, but they were very similar to those in the densest part of the latter, and where the staining was not too intense the same granular appearance could be made out in them.

Comment on Case 2.—This case had a more malignant course than the previous one, and than most of those that have been recorded. In the symptoms themselves there was nothing very unusual, but the absence of all "irritative" phenomena may be noticed. In some other ways, e.g., in the age of the patient, the duration of the symptoms, the presence of calcareous deposits in the tumour, and the favourable primary result of operation in spite of the large size of the tumour, it resembled Case 1. In its pathological aspects it had many unusual features. The tumour showed far more mitotic figures and was evidently of a more actively growing nature than any other oligodendroglioma of which I have seen a description. A more striking feature was the spread of the growth into all the ventricles. In the anterior horns of the lateral ventricles and in the fourth ventricle the deposits may have formed in one of two ways. All the strips of tumour tissue in these situations were continuous with each other and with the main mass, and so may have grown by extension of the main tumour without any breach of continuity. But in the right lateral ventricle, at the junction of its posterior and inferior horns, there were two little bosses of tumour quite separated from any other growth. These must have arisen from " seeds " of tumour carried in the cerebrospinal fluid and deposited on the ependyma—i.e., they are metastases. Several features of the strips and bosses of tumour in the rest of the ventricular system make it likely that they, too, arose largely as metastases from tumour cells carried by the cerebrospinal fluid. They lay along the floors of the horns where deposits from the fluid are likely to fall; their blood-vessels came from the underlying tissue and not from the direction of the main mass; and judging from their fairly uniform thickness the proximal parts were no older than the distal.

The structure of these small masses evidently shows how oligodendroglioma may grow when freed from mechanical pressure. The tissue is very loosely formed and to the naked eye has a glistening or translucent appearance. But the most remarkable feature is the evident branching of the cells and the apparent formation by them of a delicate supporting framework for the growth. Where the cells were packed closely together, as in the main tumour and in certain sections of tumour in the fourth ventricle, no branches could be seen; but where the formation was much more open, e.g., at the anterior end of the fourth ventricle, and, in particular, in the delicate strands of growth in the aqueduct of Sylvius, the network of fibres, and to a less extent the cytoplasm round the nuclei, were visible in all the sections. Where they took up an adequate amount of stain, as in the sections prepared by Mallory's method, the appearance of the cells and branches corresponded closely with those in the pictures of oligodendroglia given in Penfield's paper [7], with the exception that the branches of the cells seemed to join together to form a network. If the cells and branches are of an oligodendroglial nature it is apparent from their staining reactions that they are not fully developed oligodendroglia. They may belong to an incompletely differentiated stage. Other observers have not found such branches in oligodendrogliomas, except by using special staining methods. But in these loosely formed ventricular tumours the amount of fibre formation is likely to be greater, and certainly the opportunities for observing the fibres are infinitely better, than in the usual oligodendroglioma with densely packed cells. The network is seen in this case, partly because it is unusually stainable and partly because the conditions are unusually favourable for displaying it.

Of the greatest theoretical interest also is the presence of a small nodule of growth in the scalp. I know of no established instance of tumours arising from cerebral tissue growing outside the central nervous system. In the clinical account of one of the cases of oligodendroglioma described by Bailey and Bucy it was stated that the patient when last heard of "seemed to be developing an extra-cranial extension in the neck." That was eight years after his first operation and more than a year after his fourth operation. This had not been verified anatomically, but the writers thought the observation sufficiently reliable to comment on it. There are, therefore, now these two cases which suggest that oligodendroglioma cells may have the power of propagating when implanted in a mesodermal tissue.

If this nodule was oligodendroglioma, we must suppose that it arose from tumour cells which were sown in this situation at the time of the operation, twelve and a half months before the patient's death. In that case it had taken more than a year to form a spherical mass one centimetre in diameter—a fact which indicates in a new way the slowness of growth of oligodendroglioma.

REMARKS ON THE CLINICAL FEATURES AND ON THE LIFE-HISTORY OF OLIGODENDROGLIOMAS.

Clinical records of four cases and some clinical features of nine other cases were given by Bailey and Bucy. Carnegie Dixon and Jumentié and Thomas also gave clinical descriptions of their cases. These accounts are easily available to English readers and need not be detailed. Among older records there are the cases described by Landau [6] and by Ziveri [11]. The tumour in Landau's case was composed of small glial cells having deeply staining nuclei and only an indefinite rim of cytoplasm; the margin of the tumour was characterized by an increase in the small glial elements and the satellites of the nerve cells; there were calcareous deposits in the growth. The patient was a man aged 29, who, three and a quarter years before his death, had had a few epileptiform fits. He then had bouts of headaches at long intervals. Up to the time of his death he presented no abnormal neurological signs with the exception of tremor in his left arm for a few weeks before he died. The optic discs were normal. At the autopsy the right frontal lobe was found greatly enlarged by tumour and by œdema.

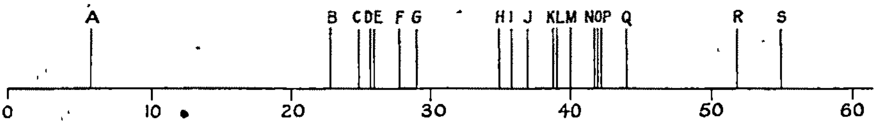
Ziveri's patient began to suffer from fits about the age of 37, and died five years later in an asylum. He became blind and deaf and had epitileptiform attacks at intervals of two or three months. He made no complaint of headache and had no vomiting. There was no loss of power in the limbs and no changes in the reflexes. Shortly before his death the patient had paralysis of voluntary conjugate movement of the eyes to the left, slight bilateral exophthalmos and bilateral anosmia. The tumour occupied the right prefrontal lobe and the anterior part of the temporal lobe. The cells composing it were small and of uniform size; their nuclei were rich in chromatin but their cytoplasm stained only faintly and with difficulty. In the margin of the growth there were "numerous granular cells evidently derived from the third element." In the histological description there is no mention of calcification.

With the two cases described here there are in all nineteen clinical accounts on which we can draw.

In sixteen cases the tumour lay laterally in the cerebral hemispheres in a situation where it did not interfere directly with the circulation of the cerebrospinal fluid. Evidently oligodendrogliomas have a tendency to lie in the frontal and parietal lobes, for only one of these sixteen tumours was temporal and one occipital.

In three cases the tumour lay across the middle line of the brain—in one (Carnegie Dixon) [4] in the floor of the third ventricle, in another (André-Thomas and Jumentié) [1] passing across from one lateral ventricle to the other, and in the third (Bailey and Bucy's Case 3) [2] growing in the septum lucidum. These three cases separate themselves sharply in their clinical features from the others. Their symptoms began at an earlier age, the course was much shorter, there was no calcification in the tumours and the results of operation were unfavourable. These cases must be considered atypical. In central situations the nature of the growth has little opportunity to influence the clinical course, and the clinical condition is dominated by the features of hydrocephalus. Consequently these three cases will not help us towards the clinical recognition of cases of oligodendroglioma, and we need give them relatively little consideration.

AGE OF THE PATIENTS.



	Age	Case		Age	Case
A	6	Carnegie Dickson.	K	39	B. and B. Case 4.
B	23	André-Thomas and Jumentié.	L	39	B. and B. Case H. C. G.
C	25	Bailey and Bucy. Case 3.	M	40	Martin. Case 2.
D	26	Landau.	N	42	B. and B. Case 1.
E	26	B. and B. Case P. E. M.	O	42	B. and B. Case 2.
F	28	B. and B. Case 6.	P	42	B. and B. Case 7.
G	29	B. and B. Case Hans G.	Q	44	B. and B. Case 9.
H	35	Martin. Case 1.	R	52	B. and B. Case 8.
I	36	B. and B. Case 10.	S	55	B. and B. Case Mary D'A.
J	37	Ziveri.			

The marks on the accompanying diagram indicate the ages of the patients at the time of the onset of their symptoms, and it is at once clear that oligodendrogliomas are tumours of the middle third of life. In 84 per cent. of the cases (16 of 19) symptoms began between the ages of 23 and 45.

Of the sixteen tumours which lay in the cerebral hemispheres away from the middle line, none produced symptoms till after twenty-five, and the average age at the onset was 38. Two tumours did not manifest themselves until the patients were over 50, and it is worthy of note that these were both situated in "silent areas" in the right cerebral hemisphere. All the others began to cause symptoms during the age-period 25 to 45.

The three tumours which lay in the middle line produced symptoms before the age of 25, the average age of the patients at the onset of symptoms being 18.

If we consider the age of the patients by the time they came to operation, we find that in the tumours of the "hemisphere" group the average was 43, with extremes at 33 and 56; in the "mid-line" group the average was 18, the extremes being 6 and 25.

In both the cases recorded here the patients had had symptoms for three years before severe signs of intracranial pressure came on and in other cases of the "hemisphere" group described by Bailey and Bucy, intervals of ten, eleven, and even seventeen years have elapsed before increasing intracranial pressure rendered operation necessary.

The average period which intervened between the first symptom and operation (or death) in the sixteen cases in which the tumour lay clear of the middle line, works out at four years and nine months, the maximum being seventeen years and the minimum eight months. Even neglecting the extreme case in which the interval was seventeen years, the average was nearly four years.

Little need be said in regard to the actual symptoms since these depend more on the situation of the tumour than on its nature, but the quality of the symptoms call for comment.

Severe paralytic phenomena were conspicuously absent throughout the whole series of cases. Even in two of Cushing's cases in which the tumour involved the pre-central gyrus, weakness of the face and slight aphasia were the only symptoms of defect. In one case, where the tumour was occipital, homonymous hemianopia was found on examination about ten years after symptoms had begun, and in my second case slight unsteadiness in the right arm and leg were associated with a large parietal tumour. But with these exceptions "deficiency" symptoms of any severity were absent from all the fully recorded cases. This fact prompts the thought that the growing oligodendroglioma compared with other gliomas must cause little destruction of the brain tissue of the host.

On the other hand, "irritative" phenomena were frequent. Generalized convulsions were one of the earliest symptoms in five out of the eight cases of "hemisphere" tumours of which a history is available, and visual Jacksonian attacks were for ten years the only symptom in a sixth case (Bailey and Bucy, Case 12). Motor Jacksonian attacks seem to have occurred in one case only, and in that instance twitching was confined to the right side of the face and neck. Petit mal attacks occurred in two cases. Several of the patients were treated for years as cases of epilepsy.

Headaches seem to have been the first symptom in about one-third of the cases of hemisphere tumours. In my first patient the pressure of the cerebrospinal fluid two years after the onset of the headaches was found to be only 145 mm. of fluid, so that headaches can hardly be attributed to increase of the general intracranial pressure. Local displacement of cerebral structures from occasional swelling of the tumour must be held a more likely cause. In conjunction with this view the fact that the tumour was degenerated must be borne in mind, and it is doubtful whether any of these tumours caused symptoms until degeneration had occurred in them.

Long periods of complete remission of the symptoms were a feature of several cases. In the third year of his illness my first patient had a period of nine months in which he had not even a headache, and this freedom extended up to within a few weeks of the outburst of intense signs of intracranial pressure. Landau referred to two similar remissions in his case, and other instances are found in Bailey and Bucy's Cases 1 and 4. These remissions also must be correlated with physical changes in the tumours associated with degeneration.

The feature most likely to bring the possibility of an oligodendroglioma into consideration in a case of cerebral tumour is the X-ray appearance. With modern radiological technique calcification within the tumour has been visible in the films in all the cases of oligodendroglioma of this "hemisphere" or "lateral" group. In the three cases of mid-line tumours no calcified shadows were seen.

The chief feature in a good film is an irregular stippling, coalescing in places to produce wavy streaks or a moniliform appearance. Isolated flecks of calcareous deposit may also be seen and in the stereoscopic picture a mass of the tumour may be faintly indicated by an opalescent appearance, although one cannot say that any definite calcareous shadow is present in it. The deposits are in the central part of a mass of which the limits are vague. For the detection of the calcified deposits the quality of the X-ray films is of the greatest importance. This is emphasized by the experience of my first case in which they were recognized eleven months later, not because they had materially increased but because the films were much better. In two of Cushing's cases examined before the introduction of the Potter-Bucky diaphragm no calcareous shadow was seen.

Calcification in intracranial tumours is not very uncommon. The subject has been studied by Van Dessel [10], who reviewed the cases radiographed at Cushing's clinic in the years 1921-1925. Among 126 cerebral gliomas, there were seventeen (13 per cent.) in which some calcification was visible. The shadows fell into three types. Most common were irregular streaks; in a few cases there were curved lines suggesting that the deposit lay in the wall of a cyst; while the third type, of which there was only one instance, was "massive." The first type of shadow was shown by thirteen tumours (10 per cent.) and four of these were oligodendrogliomas, the remainder being astrocytomas and neuroblastomas. Differential diagnosis of the nature of the tumour by means of the shadow is not possible because the calcareous deposits lie chiefly in the walls of the arteries and capillaries.

Calcification takes place presumably during the latter years of the tumour's life. The oligodendrogliomas which have been described at the earliest stages (mid-line tumours) showed no calcification although they were already large and partly degenerated. The age of the host is almost certainly an important factor in this process, for Hurst [5] found in a great variety of other cerebral conditions that calcification was rare before the age of 30. The oligodendroglioma which lies across the middle line of the brain causes hydrocephalus and brings about the death of its host before either tumour or host is of sufficient age for calcification to occur.

The colour of the tumour when seen at operation in my cases was dark red with a blue tinge; when removed and cut the tissue appeared lighter—"pinkish-blue" or "light plum" coloured. Bailey and Bucy described the tumour in one of their cases as "reddish gray." Bailey and Cushing [3] commented on this point as follows: "They are tumours of peculiar appearance, sometimes showing a pinkish colour on fresh section, and they could hardly be mistaken for any other lesion unless possibly for a neuroblastoma." Carnegie Dixon [4] described the colour after fixation as "pinkish brown." The large necrotic centre of hæmorrhagic colour with a "cortex" of "fleshy" consistence may also help in the recognition of these growths.

Microscopical examination of the margin of the growths shows that they do not infiltrate at all widely and that a few millimetres away from the edge of the tumour the brain tissue is apparently healthy (fig. 7). But the tumours encountered at operation are large masses of irregular outline, and it would be impossible to remove every particle of the tumour and of the transition zone, however narrow, unless one removed at the same time a wide margin of healthy brain. They are, however, relatively favourable for palliative operation, and the primary results obtained have been excellent.

Having regard to the long pre-operative phase and the immediate results of operation, the post-operative period in my cases was somewhat disappointing. The first patient remained well for more than a year and then died with symptoms which indicated an extension of the tumour in the inferior part of the left frontal lobe. The second patient was re-admitted to hospital within nine months of his operation with a recurrence of his former symptoms and died four months later.

The fact that the average interval between the occurrence of the first symptom and the time of operation was nearly five years demonstrates that oligodendrogliomas, at any rate, when they lie in the cerebral hemispheres, are tumours of slow growth. Moreover, calcification is the expression of an extremely chronic degenerative process, and all the "hemisphere" tumours which have been described were already partly calcified by the time they were discovered.

The supposition that many of these tumours have been present for a very long time before their discovery, is supported also by the great difference in the age at which symptoms appeared according to the situation of the growth relative to the channels of the cerebrospinal fluid. The mid-line tumours because of their obstruction of the cerebral fluid circulation caused symptoms early; they gave evidence of their presence at the average age of 18. But the tumours in the cerebral hemispheres did not manifest themselves till the average age of 38—a difference of twenty years. Neglecting the quite exceptional case of Carnegie Dixon, the difference between the average ages at operation in the two groups is eighteen and a half years. The suggestion is that if one of these growths lies in such a position that it does not readily obstruct the cerebrospinal fluid circulation, it goes on, before compelling operation, for eighteen and a half years longer than if it is so situated as to cause obstruction early. While this last argument may not apply without modification to all cases, e.g., to my Case 2, these various considerations do nevertheless suggest that the life of the tumour is so long that the beginnings of pathological growth are in most instances to be referred to the early adult life of the host.

SUMMARY.

(1) Two cases of oligodendroglioma are described. The first corresponded closely with previously recorded cases, but the second ran a more malignant course and pathologically showed a number of extraordinary features. Small masses of growth were found throughout the ventricles, and the cells in these ventricular growths showed branches. A nodule of growth was also found in the scalp in the base of the operation flap.

(2) The clinical features of these and the previously-recorded cases are reviewed. The cases divide themselves sharply into two groups, according to whether the tumours lay in the cerebral hemispheres away from the middle line, or whether they lay across the middle line, thus interfering with the circulation of the cerebrospinal fluid at an early age.

(3) The former group consists of sixteen cases; in them symptoms began on the average when the patient was 38, the extreme ages being

25 and 55; in seven-eighths of the cases symptoms began during the age period 25 to 45; severe paralytic symptoms were conspicuously absent, and "irritative" symptoms were frequent; operation was not called for on the average until four and three-quarter years after the onset of the symptoms; in both the cases recorded here the interval before operation was three years; absolute remission of symptoms for nine to twelve months was a feature of several cases; calcification visible by the X-rays has been present in all the cases of this group examined by modern X-ray methods. At operation, the growth in both my cases was visible on the surface of the brain, and showed an unusual bluish-red colour. The primary operative results in nearly all the cases were excellent. Recurrence of symptoms has occurred, however, in my cases thirteen months and nine months after operation, and both the patients have died.

(4) The "mid-line" group consists of three cases: in them symptoms appeared much earlier—before the age of 25, the average age being 18, with extremes of 6 and 23, the pre-operative period was short (3 to 9 months), no calcification was present in the tumours, the results of operation were unfavourable.

(5) The site of election of oligodendrogliomas is in the frontal and parietal lobes. In many instances the tumour probably begins to grow in early adult life. The nature of the symptoms to which it gives rise prompts the suggestion that during growth it does not cause much destruction of cerebral tissue. The "hemisphere" tumour becomes lightly calcified during the latter part of its life, but the "mid-line" tumour compels operation or causes death too early for deposits of calcium to occur in it.

I wish to express my thanks to Dr. Hinds Howell for allowing me to study and record Case 2, and to Dr. J. G. Greenfield, for his constant help in the pathological examination of the tumours, and for the photographs.

ADDENDUM.

Although, as has been said, no other cases of oligodendroglioma were found in the National Hospital records of the last ten years, it happened that while this paper was awaiting publication three cases of this kind, and most probably a fourth, were admitted to the hospital within a few weeks. They conformed closely to the description that has been given.

In the first case the tumour was in the left frontal lobe. The patient was a man of 44 who had been subject to occasional fits for fifteen years; he had had periods of freedom from symptoms lasting several years; headaches had been troublesome for the past year and the right leg had become slightly weak. In the X-ray picture there were heavy flecks and streaks of calcification. Nearly all the tumour was removed by operation and the patient made an excellent recovery.

In the second case also the tumour was in the left frontal lobe. The patient was a man, aged 38, who for about a year had been getting mentally inert and complained of general loss of energy. No fits had occurred. He had signs of high intracranial pressure but no paralysis. The X-ray films showed an indistinct stippled shadow of calcification above the left orbital plate. The tumour found at operation was a very large one, and its removal was followed by a fatal result a few days later. In connection with this case it may be observed that in general the history of symptoms is shorter if no "irritative" symptoms occur.

In the third case the nature of the tumour was not confirmed histologically, but its other features seem to warrant its inclusion here. The patient was a man, aged 33, who had had fits off and on for three and a half years, and recently had had occasional severe headaches, with vomiting, and slight weakness of the right face and hand. The X-ray pictures showed calcified deposits scattered throughout a volume as large as a cricket ball occupying the site of the left pre-central and post-central gyri and their underlying white matter. A better demonstration could hardly be given of the scarcity of defect symptoms in association with these tumours. Removal of the growth was obviously inadvisable and only decompression was done. The tumour was seen presenting on the surface of the brain and it had the bluish-red colour seen in cases of oligodendroglioma.

The fourth case belonged to the "mid-line" group. The tumour filled the posterior part of the third ventricle and sent a tongue down into the aqueduct of Sylvius. The patient was a girl, aged 16, and the clinical features were those of hydrocephalus. The patient had always had a large head, but symptoms had only been present for ten to twelve months. Death occurred twenty-four hours after ventriculography. There was no calcification in this tumour.

I am indebted to Dr. Collier, Dr. Adie and Dr. Grainger Stewart for permission to refer to these cases, and again to Dr. Greenfield.

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CUTANEOUS TACTILE LOCALIZATION.

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I.—THE SUPPOSED PATHWAY FOR CUTANEOUS LOCALIZATION.

NORMAL persons are able to localize the site of cutaneous stimulation with a degree of accuracy which varies with the part of the body surface stimulated. This faculty has been investigated by many workers, including v. Frey, Head, and more recently Stopford, and the current ideas with regard to the mechanism which underlies it embrace a detailed scheme of peripheral and central pathways. Definite localization fibres in the peripheral nerves, connected with end-organs which respond to any form of stimulation in their immediate vicinity, are supposed to pass into the spinal cord where they continue upwards towards the brain in a tract distinct from that of cutaneous discrimination. In the brain-stem the impulses subserving tactile localization are supposed to become separated off from the associated tactile impulses and, after passing through the thalamus, to have cortical representation.

Localization is regarded as belonging to the epicritic group of sensibilities. It is held that after section of a peripheral nerve localization with the rest of this epicritic group is lost over a greater area, and is recovered later, than is the group of protopathic forms of sensibility. The pattern of the sensory impairment resulting from this dissociated loss of the "cruder" and of the "higher" forms of sensibility after nerve section is explained upon a purely peripheral factor—a difference in the distribution of the cutaneous fibres subserving the protopathic and epicritic forms respectively. Attempts have been made to account for the changing conditions found during the process of nerve regeneration in terms of a difference in the rate of recovery of nerve fibres concerned with these two supposedly different types of sensibility. A difference in their rates of growth, for example, has been postulated by Ranson, but Stopford considers that the evidence in favour of this explanation is insufficient [22, p. 374], and refers us to the other end of the hypothetical localization pathway, to the cerebral cortex, for the elucidation of this problem.

Thus the considerations invoked to explain the delay in the return of the ability to localize cutaneous stimuli and those invoked to explain the wider loss are totally different, but an attempt is made to soften this disparity by the reflection that "on general grounds it seems only reasonable to expect to find an explanation of the two stages of recovery in the cerebral hemisphere, and such a view has the added attraction of illustrating once again that the functions of the nervous system are integrated on the principle of evolution" [Stopford, 22, p. 378]. The inconsistency of this step is masked by the observation that it involves a "sound physiological principle" [Stopford, 22, p. 377], since "ultimately we must of necessity turn to the sensory cerebral centres for any explanation of the changes in consciousness induced by various stimuli" [Stopford, 22, p. 377].

Apart from other implications of the protopathic and epicritic hypothesis, this view of the nature of cutaneous localization entails the following suppositions which, for reasons about to be given, must be considered to be invalid.

There must be a specific end-organ which responds to a specific attribute of the stimulus applied—its position on the body surface (its "immediate vicinity"). It is difficult enough to imagine the essential character of a purely painful stimulus apart from mechanical, thermal or chemical agencies; it is a form of stimulus which can be defined only in terms of the sensation which its application evokes. A localization stimulus in the same sense is a verbal fiction.

The fibres which are activated by the "site" of the stimulus convey to the cerebral cortex impulses which are there interpreted as local signs; interruption of their messages allows the recognition in the cortex of sensations of touch, heat, &c., but without any accurate indication of the whereabouts of their peripheral origin. Stimulation of these fibres and tracts ought therefore to lead to a sensation of "there-ness" without any conception as to what is happening "there." Now although in certain cases of diminished cutaneous sensibility a person may be able to localize with accuracy a stimulus without being able correctly to describe its nature, yet the stimulus appears to be of some definite form particularized by the subject of this sensory examination. He will say, "I cannot be sure as to what it is but it feels as though. . . ." something or other were happening. In other words, a sense of localization divorced from any sense of quality does not occur, and it would not be expected to occur because we can no more conceive of a sense of "site of stimulation" apart from a stimulating object than we can conceive of the idea of space as a pure representation apart from any impression.

Yet the fact remains that given an adequate stimulus there is produced in the consciousness of any normal person a twofold sensation corresponding to the nature of the stimulus and to its point of application, the recognition of quality and of localization, an impression and a judgment, and some more acceptable view of the factors underlying this judgment is required.

II.—THE LOCALIZATION OF TOUCH.

Although touch has received more than current mention in nearly all works dealing with sensation, the only definition or description is given by Trotter and Davies [25]. These authors describe the sensation of being touched as that of receiving a superficial "minute pat" within a small, well-defined area; it never feels heavy and is accurately localizable [25, p. 158]. They also agree with v. Frey [10, p. 95], who pointed out that the sensation arises at the moment when contact of a suitable agent with the skin is made and again when it is interrupted. The sensation of touch, whenever evoked, has invariably the same characteristics; thus, in areas of diminished but recovering sensibility, touches, although elicited only by a heavy bristle which pits the skin, resemble the same superficial pat within a small but well-defined area [25, p. 158]. An important characteristic of this same form of sensibility is lack of quantitative variation. With true touch, "if the stimulus fails to produce a perfectly distinct, fully-developed sensation it is not felt at all [25, p. 158]. Although changes in other stimuli may produce variations in the intensity of the other sensations aroused, "no such continuous series of intensities can be produced for touch" [25, p. 158].

The sense of touch has in this and in other ways to be sharply differentiated from the sense of pressure. Both may be originated by mechanical stimuli applied to the skin without affecting the subcutaneous structures [25, p. 222], but it is held that they "cannot be regarded as forming a continuous series with the sole distinction of degree in the force of the stimulus," but are subserved by independent "physical and physiological mechanisms." Pressure, besides its sense of "heaviness," increases with perseveration of the stimulus alone and gives rise to only a "vague idea of extent or locality" [Trotter, 25, p. 158].

Upon the observations of touch in areas of normal, hypoæsthetic and recovering sensibility have been based various theories in regard to the nature of this sensation. Trotter and Davies have laid it down that any theory to be acceptable must provide an adequate explanation for tactile hypoæsthesia, and it is in this respect that many fall short of the requirements. To remedy this defect these authors have themselves made the following suggestions as to the essential nature of the tactile mechanism. Touch and pressure sensations are both responses to mechanical deformation of the skin, but each is subserved by an independent physical and physiological mechanism. The essence of the stimulus giving rise to touch is movement, that of the stimulus giving rise to pressure is compression, i.e., the essence of the touch stimulus is rate of change, reflected in its dependence upon its time relations, that of pressure is "static contact."

Since the conceptions of "change" and "maintained alteration" are so fundamental to the distinction between touch and pressure, it is worth while pointing out that the word "contact" used in this context is apt to give rise to confusion. When two objects have contact each with the other they may be supposed to be in a condition of contiguous juxtaposition, i.e., in common parlance, "just touching." There is no suggestion as to any forces normal to the surfaces of contact, i.e., no pressure or deforming force exerted between them. In this sense, the only difference between "moving contact" and "static contact" would be one of duration only, the former occurring instantaneously and the latter for a varying period. In so far as an object applied to the skin, if it is to evoke a sensation either of touch or of pressure, must bring about some local deformation, however slight, its relation to the *surface* may be that of contact, but its relation to the *body* must be that of a deforming force. It is not the contact as such, but the slight deformation which sets up the impulses giving rise to the sensation of touch. It seems probable that in an attempt to provide additional emphasis for the most important distinction between touch and pressure, Trotter and Davies have strained contrast unduly, for their observations have led them to "expect to find in the physical mechanism of touch means whereby *movement* is very directly transformed into a nervous impulse" [22, p. 218]. It is inconceivable that movement, as such, should be transformed into nervous impulses apart from any secondary effects of movement such as resulting tensions or compressions within the body. Even if, as they suggest, it is the movement of a hair-bulb away from the surface which initiates the nervous impulses, the argument still applies, because the body would take no account of movement of the hair-bulb apart from resulting forces exerted upon structures within it (the hair-bulb) or without it, any more than it would of the passage of a bullet or a knife through the tissues apart from the compression and tearing effects produced. Moving contact and static contact are perhaps unhappily chosen terms for these characteristics, but the difference which underlies them is clear and more definite than the obscurity of the phrase "the contact of tactile pressure" [Stopford. 21, p. 407] would lead one expect.

In view of these considerations, it appears that mobility alone, whether of the skin or of the hair-bulb, cannot determine the sensitivity of the surface. In addition to this difficulty in regarding the touch stimulus as differing in quality from the pressure stimulus, there are other reasons for disbelief in a specific tactile mechanism in the skin. Thus, although the cornea of the eye has been usually held to give rise only to pain sensations as the result of any adequate stimulus, Goldscheider and Bruckner [12] have found that a sense of contact, although obscured in most subjects by pain, can be perceived by some and can be in others unmasked by cocainizing the cornea lightly.

Although the neighbourhood of the hair-bulbs is especially sensitive to light touches, these can also be felt when a stimulus is applied remote from the hairs and even on areas unprovided with hair. Therefore, there is evidence to show that a sensation of touch may be elicited by very light stimulation of a structure, such as a naked nerve-ending, which with degrees of stimulation usually encountered during life give rise to pain. The above observations on the sensitivity of the cornea support this view, and simpler animals respond to very light stimuli such as give rise in man to the sensation of touch (although no inference can reasonably be drawn as to sensation in them) from surfaces where the cutaneous receptors are limited to free nerve-endings or to a very few pacinian corpuscles [15, p. 73]. Moreover, Adrian has shown [3, p. 49] that in the frog and in the cat free nerve-endings can give rise on light stimulation to a brief outburst of impulses characteristic of touch, and on slightly stronger stimulation to a continuous, prolonged stream of impulses characteristic of pressure or of pain. In the cases where, using a mechanical stimulus, impact produces touch and pain impulses, and pressure produces pain impulses only, Adrian brings forward evidence to show that the stronger stimulus does not activate additional end-organs but stimulates the same end-organs to a further degree. The lightest effective touch produces an outburst of impulses lasting for a fifth of a second only. This is due to rapid adaptation of the receptive structure or end-organ. Pain discharges in the peripheral nerve are characteristically prolonged and probably give rise to the appropriate effective response in the central nervous system by virtue of this extended duration which provides successive summation at some central synapse.

Therefore there is good reason to believe, (1) that although in the neighbourhood of the hair-bulbs the conditions are especially favourable for the initiation of a disturbance interpreted centrally as touch, yet they provide only local intensification of a responsiveness which is more widespread, and (2) that the difference between the types of discharge underlying touch and other forms of cutaneous sensibility is one of degree only.

The characteristics of the touch which is derived from the normally innervated skin are shared by that which reappears with regeneration of a previously divided peripheral nerve. Authorities differ as to the form in which touch reappears. The explanation of this discrepancy in results lies probably both in the method of testing and in the subjective analysis of the sensation aroused. But the fact of significance which stands out and as to which all authors agree, is that as soon as such a stimulus becomes adequate, the sensation elicited, whether that of true touch or of pain, is endowed with a local sign. Even when associated with pain, this local sign is sufficiently well marked for Schäfer to note both local and peripheral reference, and when associated with touch it is so emphatic that Trotter and Davies comment upon the surprising precision with which the part involved may be described. Thus, tactile stimuli, as soon as they become adequate, give rise to a sensation having local signature associated with an impression determined by the method of examination and standards of reference used.

III.—THE RELATION BETWEEN TOUCH AND LOCALIZATION.

The sense of touch has been shown by Trotter and Davies to be a well-established and distinct form of sensibility having certain well-recognized characteristics, distinguishing it from all other forms of sensibility, including pressure. It has also been argued in the previous section that there are no adequate grounds for regarding the peripheral mechanisms of touch and pressure as being distinct. The peripheral nervous mechanisms appear to be identical, the sensations aroused are subjectively very different. It may well be asked what it is that endows the sense of touch with a character so sharply distinct from that of pressure.

The peculiarities of the touch sensation, which cannot be ascribed to a special peripheral mechanism, must depend upon some peculiarity of the central response. The characteristic of the central response or sensation is the association with the impression (of touch) of a judgment (localization). The view which it is the purpose of this paper to advance, is that the function of what is generally called the sense of touch is localization; accurate localization apart from touch does not exist as a sensory impression, but only as a theoretical concept. It is maintained that an examination of the characteristics of the sense of touch shows that it is indissolubly linked with that of localization, and that no other function than this can reasonably be ascribed to it.

Trotter and Davies have drawn attention to the unnaturalness of the sensation of touch as derived from experimental observations "when we remember how rare in ordinary life is any practice in the discrimination of slight touches passively received" [25, p. 142]. v. Frey states that in this sense (of touch) a light pressure is never or only under special circumstances a *transitory* sensation [10, p. 95]. Yet since the sensation of touch is a reality when sufficient care is given to its recognition, and since also all "sensation has developed in man to keep him precisely informed as to the nature of his customary environment" [25, p. 142], there must be some significance in its existence.

v. Frey has pointed out [10, p. 95] that our body surface is constantly subjected to mechanical changes which are of much greater degree than those which are used to elicit the sensation of touch. The pressure of air and of water from outside, and the tension changes produced by the blood-vessels and the pull of connective tissues do not normally enter consciousness because the stimulus is simultaneously applied over a wide area; such changes are appreciated immediately they are localized ["ortlich begrenzte," 10, p. 95]. Generalized pressure evokes no sensation; localized pressure evokes a sensation, not because the quality of the impression is different, but because it is associated with a local sign.

The particular stimulus used to elicit the sensation of touch is never appreciated unless localized in its application. The significant characteristic of the stimulus of touch lies in its restriction in extent, i.e., its localization. The significant characteristic of the sensation aroused by this stimulus is the recognition of this restriction, i.e., of its localization.

Thus, the characteristic stimulus provided by a minimal local deformity of the body surface sets up a very brief neuronic discharge leading to fugitive sensation in which two factors, a judgment and an impression, are mingled. The former, the recognition of the site of stimulation, has been shown to stand out with surprising emphasis. The latter only reveals itself upon careful introspection. It is here suggested that the former element is the significant one, and that the latter element has become grafted on to it as the artificial product of sensory examination with an " unnatural " stimulus.

If this view is correct, it follows that the characteristics of the form of sensibility known as light touch should be shared by the faculty of localization, i.e., accurate localization of cutaneous stimulation should be possible when the sensibility to touch is present and in abeyance when this form of sensibility is absent. Further, localization should share with sensibility to touch its independence of variations in the stimulus strength, i.e., it should not show a graded variability with changes in the stimulus, and hypoæsthesia in respect of localization should consist in a higher threshold value for stimuli capable of arousing a localizable sensation but not in the less accurate localization of a given stimulus.

It should be noted that it is not here implied that localization of all peripheral stimulation is provided by the mechanism of light tactile sensibility alone. Probably all adequate stimuli, whatever their nature, initiate a centripetal afferent discharge which bears some form of local signature, but it *is* suggested that it is only when the form of stimulation involves mechanical deformation of the skin that localization is accurate.

A series of three experiments was devised with a view to testing the inferences drawn from this hypothesis. In the first two the relation between the accuracy of cutaneous localization and stimulus-strength was investigated. In the last the accuracy of localization of stimuli involving mechanical deformation of the skin was compared with that of stimuli free from such deforming effects.

Experiment 1.—The error of localization of stimuli delivered with a graded series of v. Frey hairs was measured. The sensibility of the dorsum of the hand and fingers was examined and an apparatus was used to lower the hair on to the skin at a uniform and constant rate. Hairs varying from 50 to 4,000 mgm. bending-pressure were prepared, and of these four were selected having maximum bending-pressures of 120, 225, 450, 1,440 mgm. Ten stimulations were made with each hair and the errors of localization averaged in each case. It was found that for the ten normal persons examined, out of ten stimuli delivered with the 120 mgm. hair, on an average four were not appreciated at all. The results are summarized in the following table.—

TABLE I.

Subject	Hair 120	Hair 225	Hair 450	Hair 1,440
F.	4·5	4·5	7·0	5·0
C.P.	3·4	3·5	5 3	4·1
S.	6·5	5·2	5·4	4 7
N.P.	5 1	6·7	5·5	5·2
S.T .. .	5·7	5·8	7·6	4·5
L.B.	7·2	5·8	6·4	5·5
A.K.	4·3	4·0	6·2	5·0
N.	3·4	4·6	4·6	4·1
C.L.	3·7	5.6	4·8	4·9
P.L.	6·0	5·3	7·2	6·2
Average ..	5·0	5·1	6·0 *	4·9

* The fact that this figure is so much higher than the other average values is probably due to a defect in method: it is interpreted as due to the fact that each subject examined was stimulated with this series (450 mgm. hair) of stimulations first before the lighter and less easily appreciated hairs were used, i.e., the subjects were less "trained" in the method of the experiment than for the other hairs.

From this table it will be seen that although with weaker hairs several stimuli were not recognized, the error of localization of the stimuli appreciated was not reduced by increasing the stimulus-strength. (See Appendix, p. 366).

Table I giving the error of localization, measured in centimetres, shown by each of ten normal persons when stimulated with four v. Frey hairs of varying strengths—measured in milligrams of maximal bending-pressure.

Experiment 2.—In another subject the neighbourhood of the ulnar nerve at the elbow was infiltrated with novocain solution. Anæsthesia of the ulnar border of the hand and fingers developed within half an hour and persisted unaltered for three and a half hours. It passed off progressively during the following hour and a half. The localization of cutaneous stimuli was tested before injection, during maximal anæsthesia and repeatedly during the recovery phase. In the photographs, fig. 1, two areas are shown. The smaller area is that over which no stimulation of any kind was felt; the larger area is that over which stimuli, if felt at all, were less distinct than over normal areas.

Over the area where sensibility was present but subjectively diminished, the lighter v. Frey hairs were not appreciated and the heavier occasionally missed. Yet the localization of those stimulations which were appreciated was of the usual order of accuracy.

During the phase of returning sensibility successive stages were reached at which stimuli of progressively lighter hairs began to be appreciated. Records of the localization errors at each stage show that as soon as a stimulation of a given strength began to be appreciated at all it was localized with the customary accuracy. (See Appendix, p. 366.)

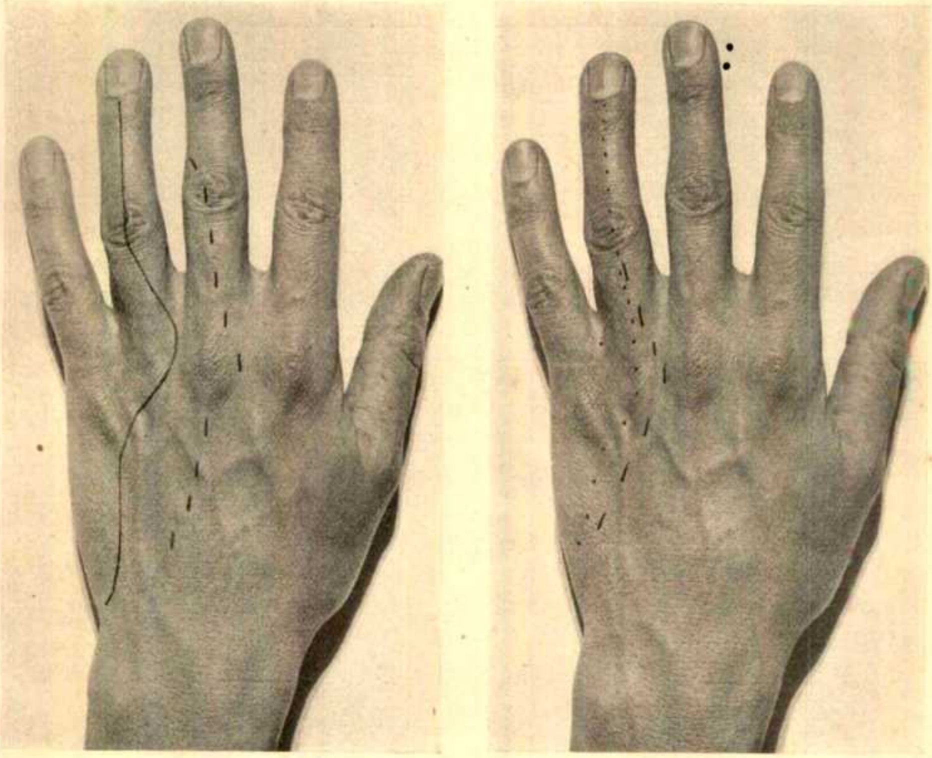

FIG. 1.—Subject S. T.

A. Time 1.10 p.m., i.e., 50 min. after ulnar infiltration with novocain.
Motor weakness: Paresis of all small hand muscles; adduction of fingers imperfect; opposition of thumb weak.
Sensory loss (shown in photograph):—
Area to ulnar side of the continuous line completely insensitive to all forms of stimulation.
Area between continuous and broken lines showed subjective diminution of appreciation of brush and pin-prick stimulation.

B. Time 4.50 p.m., i.e., 4 hours 30 min. after ulnar infiltration.
Motor disturbance shown only by slight weakness of adduction of thumb.
Sensory loss: Over area to ulnar side of dotted line pin-prick felt but not sharp; over area between dotted and interrupted lines pin-prick felt as sharp but light touch subjectively impaired.

Experiment 3.—The dorsal surface of the hand and fingers was stimulated by approaching a source of heat at various points. The skin was not touched but the nearness of approach and the duration of the stimulation were adjusted so that a distinct feeling of warmth was appreciated in the neighbourhood of the stimulus. The error of localization of the point maximally warmed in this way was measured in the same way as was used for the recording and measurement of tactile stimulations. The error of localization of such stimulations is shown in Table II.

TABLE II.

Subject	Average error of localization of ten stimuli
F.	12 mm.
C.P.	9 ,,
S.	8 ,,
B.P.	10 ,,
S.T.	6 ,,
L.B.	12 ,,
A.K.	15 ,,
N.	9·5 ,,
C.L.	10 ,,
P.L.	13 ,,

From these results it can be seen that the error of localization of this form of stimulus, not involving any mechanical deformity of the skin, is much greater than the error of localization of tactile stimulations. (See Appendix, p. 366.)

From these three experiments it is inferred that:—

(1) Accurate localization is present whenever sensibility to touch is present and is absent when sensibility to touch is absent. Also the characteristics recognized as belonging to touch are shared by localization.

(2) Stimuli which do not mechanically stimulate the skin, i.e., do not touch, are not accurately localized.

But this view, that sensibility to touch is inseparable from the faculty of localization, is not generally held. It is currently believed that responses to touch can be obtained without localization, both in lower animals and in man.

The existence in the lower animals of protopathic or dyscritic touch endowed with no local sign is a figment of scientific theory. The observations of Piéron [16], Parker [14], and others go to show that the responses which are initiated in the lower forms of life are always appropriately directed and that accuracy of localization is essential to the value of the response.

When we turn for comparison to the responses evoked by tactile stimulation in organisms at the other end of the scale of complexity, man, we find that accuracy of localization is their chief characteristic.

For not only do tactile stimuli yield precisely localized responses, whether associated, as in normal conditions, with what is described as the sense of touch or, as in conditions of recovering sensibility, with a variety of other qualities of impression, but tactile stimuli divorced from local application (not "ortlich begrenzte") are not appreciated at all.

Tactile responses in their earliest appearance, at a stage when the element of impression or qualitative aspect of sensation, as we know it, cannot reasonably be supposed to have existed, were characterized by accuracy of localization. Tactile responses in creatures of most advanced neural development are still characterized essentially by accuracy of localization.

A presure stimulus when sharply limited in extent evokes a judgment of locality. Since this locality is upon the body surface and attention is always normally attracted to it by a stimulus from outside the body, this judgment of locality is exteriorized. Now all sensations have become mentally integrated into perceptions, and these perceptions are exteriorized into the objects to which we refer as our surroundings. In the same way local signature, when presented to us by carefully controlled experiments which rob it of those impressions which in ordinary life invariably accompany it, is exteriorized and secondarily linked up with an impression (which is the re-presented product of our introspection) to form a perception, our idea of what the stimulus must have been like to have been presented to consciousness in that form.[1]

When our visual localization mechanism is abnormally stimulated the same thing happens. When a focus of irritation along the course of the visual apparatus from the retina to the occipital cortex leads to pathological stimulation, visual hallucinations are aroused. When the visual cortex itself is thus abnormally stimulated these tend to be of a gross, unorganized form; flashes of light, sheets of coloured cloud, &c. When the optic tracts are irritated and the visual cortex is intact, these hallucinations are frequently much more elaborate and highly organized.

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[1] Schäfer's experiment [19, p. 195] of placing a block of ice upon the skin overlying the ulnar nerve in his arm provides a neat illustration of this linkage of local signs due to minimal stimulation with a qualitative impression which is normally foreign to the stimulus used. He found that if the cold employed was sufficient to stimulate the fibres of the nerve below the skin, "there would be experienced a peripheral reference of sensation of an indeterminate character caused by stimulation of all the fibres of the nerve trunk to which the cold is applied." The peripheral reference was unequivocal; the sensory quality with which it was linked was indeterminate. The simultaneous activation of nerve fibres which were distributed peripherally over a wide area and which were normally never subjected to simultaneous but to successive stimulation must have provided a central disturbance with no parallel in normal experience and therefore difficult of description because unfamiliar to perception.

Things or persons are seen in certain positions and moving about in particular directions. Never does such a patient complain that his attention becomes riveted upon or drawn towards a particular direction without having any impression as to an object present or to an event occurring in that direction.

IV.—The Physiological Significance of Tactile Localization.

The capacity for localization has been shown to be intimately associated with (and it has been suggested that it provides) that form of cutaneous sensibility known as the sense of touch. Clearly the provision of this sense of touch cannot be regarded as being in any way the natural rôle of the faculty of localization. The real function of localization is that of adjusting and directing the movements which arise in response to stimulation.

Reflection shows that the sense of touch and the adjustment of motor responses are more intimately related than may be immediately obvious. For the sense of touch leads man to elaborate his perception of tactile space, and this allows him to inter-relate the relative positions of the objects around him. This perception of the spacial disposition of surrounding objects enables him to move with accuracy and safety among them. This is recognized by Parsons, who has pointed out that the essential biological function of space perception is control of movement [15, p. 146], so that these two derivatives of localization are direct and indirect views of the same thing. It is because of the characteristic exteriorization of mechanically aroused impressions that we develop tactile space perception.

A mechanical stimulus of the order of touch evokes an impression together with a local sign which leads to its being exteriorized; the more insistent the local sign the more complete is this exteriorization The sensations of heat, and cold and pain are never projected in the same degree. Perhaps it is because we are so familiar with the pain which arises from sources within our body surface that we can more readily conceive of "having a pain," or even of a part of our body being "painful" without the presence of an external causative agent, than we can of being touched or pressed upon without the presence of something external to ourselves exerting a force upon us. We become hot and cold too readily in response to change in the temperature of the air about us, or to our own exertions or sluggishness, to infer always the presence of an external source or drain of heat, and even when radiated heat is confined to a comparatively small area of our body surface we are not able to localize the stimulus with accuracy.

In the simplest of those animals which do not invariably move as a whole, but which have one or more parts of their body specially adapted for mobility upon the rest, movements are directional and adjusted with a degree of accuracy which, did we imagine them to be capable of the conscious appreciation of a sensation, would argue a developed sense of localization. Such movements of primitive animals are responses to direct stimulation; in man voluntary movements are responses, not so much to direct stimulation as to the represented images evoked by the stimulus, and are therefore directed more by that previous experience from which the perceptual content of consciousness has been built up. This is why the conception of space appears at first sight to be distinct from the control of movement.

Also in normal persons, the significance of tactile space perception is overshadowed by that of visual space perception: for sight is in this way complementary to touch, and with its aid tactile space perception achieves a scope and a significance which it could not otherwise acquire. But touch and vision have more in common than the dual provision of space perception. We have seen that the local signature of touch provides accurately directed responses of relatively mobile parts of the body at a low phylogenetic level. In the most primitive photosensitive organisms the appreciation of light is a tropism which directs the movements not of one part of the body with reference to the rest, but of the whole body in relation to its surroundings. There have thus been two parallel lines of development; that of touch which has passed from the stage of purely segmental adjustment to that of egocentric localization,[1] and that of vision which has passed from the stage of a simple photosensitive tropism to that of spacial orientation.

These parallel lines of development have taken place because both touch and vision possess another common characteristic, not merely by association but as a result of their very nature. Both are completely exteriorized. Both have to be defined objectively and not subjectively. In this, as we have seen, they stand in the sharpest contrast with pain which has to be defined subjectively and not objectively. Visual impressions are not more completely, but only more distantly exteriorized than tactile impressions, and vision leads to a representation, as far as space perception is concerned, of the same relations as does touch, but through a mechanism capable of greater precision and elaboration. When we see an object we do not merely associate visual and tactile impressions, we exteriorize and identify both in the object.

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[1] "Ontogenetically, touch builds up the egocentric self which is the point of reference," for "so-called absolute, better egocentric localization depends on reference to the body" (Parsons [15], p. 153).

Through whichever avenue it is received, localization is not a pure impression but a judgment, and the sense data of space perception which it provides become significant under comparison only. For a local sign, if it is to provide an absolute measure in itself, must be distinct from a certain part of the body surface or of the retina, even if always associated with it, otherwise it would simply be another name for "position" and not indicative of position: it would *be* position and not *signify* position. Similarly, comparison, or differences of quantitative, qualitative or motor impressions may *become* signs of external spacial relations, although not original signs provided by "space." Such differences can become signs of external spacial relations by association only, and this presupposes previous experience of their significance through some other source. Thus, comparison of simultaneous and successive visual impressions provides the means for more delicate and elaborate space perception as a result of association with the material of tactile space perception. That this correlation between visual and tactile space perceptions has to be learnt is shown, as Parsons has pointed out [15, p. 156], by those cases of cataract in which patients blind since birth have acquired vision after a successful operation comparatively late in life. We cannot assume that ideas of space may be presented alone as a pure representation apart from the impressions which accompanied the original local signs, for consciousness is built up out of impressions, not of judgments. It has been pointed out that we never have a sensation of "there-ness," or locality of stimulation, apart from an impression (accurate or inaccurate) of the kind of event which is happening "there." So also we cannot conceive of "a space" as an absolute thing apart from its material boundaries, i.e., apart from impressions. We can think of "the space within A" or of "the space between B and C," but we think in terms of the distance apart of the containing walls of A, or of the distance which separates B from C. This is why the conception of "space infinite" or limitless space, stretching indefinitely, defies the imagination, and this phrase remains an association of words without significance; imagination stretches out for ever after that further wall within which to conceive of space.

Just as the three-dimensional space of vision is built up from the simultaneous association of perceptions of distance (which is one dimensional), so is the conception of "distance-apart" of touch built up from the simultaneous association of tactile local signs, and a distance-apart is conceived of as the spacial separation of two simultaneously stimulated points (which have position but are non-dimensional).

But the mobility of our eyes and of our limbs, through the sensations aroused as the result of proprioceptive impulses received from the muscles providing this movement, enables us to adopt a more active rôle than is assumed in the above passive reception of stimuli, and to the results of *simultaneous* association are added those of *successive* association. Simultaneous association alone would only enable us to appreciate and compare surface areas by vision and linear separations by touch. Successive association enables us to conceive of three-dimensional space through both vision and touch. Simultaneity of touches, each purely qualitative and each providing an independent sense datum, is the passive element of the synthesis from which space perception is ultimately derived through the agency of movement and the accompanying proprioceptive impressions. When a succession of touches in a certain order accompany a movement, their local signature and the proprioceptive impulses consequent upon the movement automatically transform "succession" into "space." Thus the sense of touch or of localization, originating in passive reception as the controlling element in adjusted movement, comes to co-operate with movement and to be in its turn directed and applied through movement, as an active instrument for the provision of space perception.

Thus it appears that not only is tactile space perception necessary for the co-ordination and adjustment of our movements, but only accuracy in the execution and assessment of our movements makes the development of tactile space perception possible. Each is essential to the other and both are ultimately derived from a common physiological basis—the mechanism of cutaneous localization.

SUMMARY.

(1) The current view of the mechanism underlying the localization of cutaneous stimulation is described and discussed.

(2) The mechanism of cutaneous tactile sensibility suggested by Trotter and Davies is described and criticized.

(3) The view is advanced that the function of what is usually referred to as the sensation of touch is the provision of localization.

(4) A series of experiments have been made in order to test the implications of this hypothesis. It is claimed that these experiments show that:—

- (i) Accurate localization of cutaneous stimulation is possible when the sensibility to touch is present and is in abeyance when this form of sensibility is absent.
- (ii) Localization shares with sensibility to touch its independence of variations in the stimulus strength.
- (iii) It is only when the application of the stimulus used involves mechanical deformation of the skin that accurate localization is possible.

(5) Tactile responses of the simplest, as well as of the most complex animals are characterized by accuracy of localization.

(6) The physiological significance of tactile localization is discussed and its co-operation with proprioceptive judgments for the provision of space perception is outlined.

APPENDIX.

Experiment I.—In this experiment measurement was made of the error in localization of the site of stimulation with v. Frey hairs of varying strength.

The calibration of the v. Frey hairs.—The hairs were calibrated in terms of the maximal pressure which the bent hair could exert upon the pan of a balance. Each hair was held vertical over the balance pan and lowered until it just touched. The graduated rider-chain was set in a position equivalent to a weight of 2 mgm. in the other pan of the balance and the beam was released. The vertical height of the hair was then adjusted so that the pan was pressing upwards against the hair with this pressure of 2 mgm. without perceptibly bending it, and the pointer of the balance was over the zero of the scale. The other pan of the balance was then progressively loaded. The hair bent slightly more under each increase of the load until a value was reached at which it yielded and bent suddenly. The maximum load which was supported before the break occurred was taken to be the maximum bending-force of the hair. The balance used was kindly lent by Dr. C. R. Harington, of University College Hospital Medical School, and was of the "chainomatic" type, so that the load could be continuously varied over a range of 100 mgm. without any sudden increase. The final value was reached in all cases with an approximation of less than 10 mgm.

The method of testing.—For comparison of the error of localization of successive stimuli it is necessary that as the stimulating hair is moved from place to place, the only factor changed should be the spot pressed upon, i.e., the rate at which the pressure is applied must be constant and the hair free from lateral movement. The manual application of the hairs was found not to give sufficiently constant stimulations, so that the apparatus shown in fig. 2 was devised to ensure this.

The lever "A," pivoted at the point "F," is tipped slowly in an anti-clockwise sense by a weight "W" in the piston of the dashpot "D." The other end of the lever carries a small wheel which pushes up the near end of the lever "*a*" pivoted at "*f*" against the downward pull of the weight "*w*." This rotates the lever "*a*" in a clockwise sense and lowers the far end, to which the v. Frey hair is attached, with a steady uniform motion. The arm of the lever "*a*" carrying the hair is made as long as is convenient in order to give a motion to the hair as nearly vertical as possible. A second dashpot "*d*" is provided to free the lever "*a*" from those vibrations to which its great length makes it liable. The support which attaches the hair to the lever "*a*" is provided with a universal joint so that the hair can be readily adjusted over any point of a wide area.

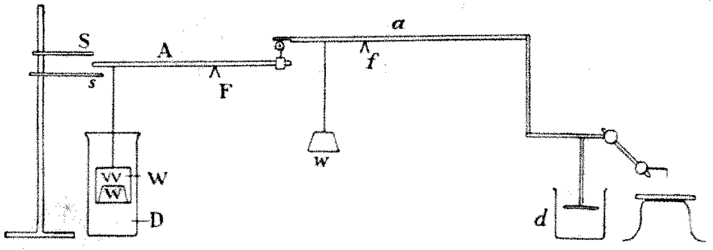

FIG. 2.

The subject tested sits with his arm fully supported so that his hand lies beneath the hair, but in such a position that the apparatus and his hand are shielded from his view. He is provided with a photograph of an extended hand which he is required to prick at points exactly corresponding to the points on his own hand which he imagines to have been touched. On a rough diagram he also indicates the approximate positions of these points by means of numbers, 1 to 10 corresponding to the ten stimuli applied. The person testing the sensibility is provided

TABLE III.

		1	2	3	4	5	6	7	8	9	10	Average error
Subject F.	Hair 120	0	10	5	7	2	3	—	—	—	—	4·5
	,, 225	0	6	7	8	4	3·5	3	5	4	—	4·5
	,, 450	0	0	8	3	3	14	11	17	—	—	7·0
	,, 1,440	0	6	4	8	2	8	7	9	2	4	5·0
Subject C.P.	,, 120	0	3	8	2·5	—	—	—	—	—	—	3·4
	,, 225	0	0	0	5	8	8	4	—	—	—	3·5
	,, 450	0	0	7	5	11	4	6	8	7	—	5·3
	,, 1,440	0	2	14	4	12	8·5	8	10	4·5	8	4·1
Subject S.	,, 120	0	21	4	6	4	4	—	—	—	—	6·5
	,, 225	0	0	9	8	8	7	6	3	5	—	5·2
	,, 450	0	0	0	6	3	11	11	12	—	—	5·4
	,, 1,440	0	0	0	4	16	4	5	6	4	8	4·7
Subject B.P.	,, 120	0	6	3	4	7	11	—	—	—	—	5·1
	, 225	8	9	9	7	5	2	—	—	—	—	6·7
	,, 450	0	4	7	6·5	10	14	4	3	4	3	5·5
	,, 1,440	0	0	0	12	9	4	9	6	4	8	5·2
Subject S.T.	,, 120	2.5	4·5	4·5	3	14	—	—	—	—	—	5·7
	,, 225	0	0	10	15	4	—	—	—	—	—	5·8
	,, 450	0	2	14	14	12	4	8	11	3·5	—	7·6
	,, 1,440	0	0	9	3	3	11	10	2	3·5	4	4·5
Subject L.B.	,, 120	12	4	8	4	12	6	4	—	—	—	7·2
	,, 225	0	9	4	11	6	3·5	8	6	5	—	5·8
	,, 450	0	0	8	4	12	12	6	4·5	10	8	6·4
	,, 1,440	0	0	7	2·5	3	10	12	8	7	5	5·5
Subject A.K.	,, 120	0	7	6	2·5	6	—	—	—	—	—	4·3
	,, 225	2	4	9	3·5	4	5	2·5	2	—	—	4·0
	,, 450	0	0	7	11	3	12	10	8	6	6	6·2
	,, 1,440	0	0	2	3	7	9	8	9	2	10	5·0
Subject N.	,, 120	0	2·5	6	3·5	7	—	—	—	—	—	3·4
	,, 225	0	0	8	12	6	2	5	4.5	—	—	4·6
	,, 450	0	3	6	6	10	4	6	3	4	4	4·6
	,, 1,440	0	0	0	9	4	8	8	3	6	3	4·1
Subject C.L.	,, 120	4	2·5	2·5	7	3	5	2	—	—	—	3·7
	,, 225	10	5	6	6	8	4	4	7	6	—	5·6
	,, 450	0	0	0	4	5	9	10	12	4	4	4·8
	,, 1,440	0	0	7	4	9	4	9	3	8	5	4·9
Subject P.L.	,, 120	0	8	4	10	9	5	—	—	—	—	6·0
	,, 225	0	0	6	3·5	5	5	4	14	10	6	5·3
	,, 450	0	11	8	12	10	7	6	4	8	6	7·2
	,, 1,440	0	0	4	6	9	9	5	10	12	7	6·2

Table showing the error in localization of stimulation over the dorsum of the hand and fingers in ten subjects, each tested with ten stimulations with each of four v. Frey hairs. The four hairs are distinguished by the different maximal bending-pressures; 120, 225, 450 and 1,440 mgm. The localization errors are recorded in millimetres :—

0 = no measurable error of localization.
— = stimulus not appreciated at all.

with a similar photograph and diagram—he pricks the photograph and numbers the diagram at the points over which he then adjusts the hair. He releases the free end of the rod "A" from the support "S" from which it falls as far as the stop "*s*." The hair is thereby lowered until it rests, fully bent, upon the skin.

The two photographs are then compared and the pricks on one are transferred to the other; the distances between corresponding pricks (determined by the numbering of the diagrams) are measured in millimetres to give the error of localization of each stimulation.

Table III gives the error of localization of ten successive stimuli delivered with each of a series of four hairs of different bending strengths.

Experiment 2.—It was decided to examine the error of localization over an area in a condition of tactile hypoæsthesia. For this purpose some means was sought of providing such an area quickly and transitorily so that the localization could be tested while the skin sensibility was normal, when it had been made hypæsthetic and after it had again become normal.

TABLE IV.—SUBJECT S.T.

Time	Hair	1	2	3	4	5	6	7	8	9	10	Average
11-11.45 a.m. ..	120	2·5	4·5	4·5	3	14	—	—	—	—	—	5·7
..	225	0	0	10	15	4	—	—	—	—	—	5·8
..	450	0	2	14	14	12	4	8	11	3·5	—	7·6
..	1,440	0	0	9	3	3	11	10	2	3·5	4	4·5
12.20 p.m. ..	Ulnar infiltration with 1·5 c.c. novocain (2 per cent. solution with adrenalin) at elbow.											
1.30 ,, ..	1,440	0	15	7	3	8	3	—	—	—	—	6
1.50 ,, ..	225	0	0	4	9	10	3·5	4	8	—	—	4·8
2.15 ,, ..	120	7	4	11	4	2·5	5	—	—	—	—	5·5
4.15 ,, ..	1,440	0	10	7	3	6	4	4	—	—	—	5
4.25 ,, ..	450	0	5	3	5	—	—	—	—	—	—	4·3
4.35 ,, ..	225	4	8	5	2·5	7	10	—	—	—	—	6
4·45 ,, ..	120	0	0	3	4	10	7	5	—	—	—	4·1

v. Frey hairs distinguished by maximal bending-pressures in milligrams.
Errors of localization with ten successive stimulations given in millimetres.
0 = no measurable error of localization.
— = stimulation not appreciated at all.

An attempt was made to adopt the means used by Stopford, which consisted in treating an area of skin with a 10 per cent. solution of cocain hydrochloride in chloroform. But a saturated solution, which was of less than 5 per cent. strength, gave no detectable hypoæsthesia after repeated tests. Therefore the cocain alkaloid, which is much more readily soluble in chloroform, was used as a 10 per cent. solution. Repeated painting of the same area of skin resulted in no detectable diminution of sensibility.

A patient whose arms were in every way normal was therefore chosen, and an infiltration of 2 per cent. novocain solution with adrenalin (in water) was made just behind the median epicondyle around the ulnar nerve. Cutaneous sensibility over the fifth finger and part of the fourth finger and of the hand rapidly showed signs of diminution; subjectively within ten minutes and to objective testing within twenty minutes. By forty-five minutes the sensory impairment was maximal and its extent is shown in fig. 1, p. 359. The error of localization of stimulation with a v. Frey hair was measured before the injection was made, while the sensory impairment remained maximal and repeatedly as it was wearing off. The results are shown in Table IV.

Experiment 3.—An attempt has been made to compare the error of localization of stimulation with some form of stimulus not involving any mechanical contact with the skin, with that of tactile stimulation. Heat seemed the only form of stimulus fulfilling this requirement, and some means had to be found of supplying heat to a sharply localized area of the skin. No convenient means suggested itself for focusing a distant source of heat on to different parts of the skin in reasonably rapid succession; although such a means would be ideal for the purpose.

TABLE V.

Subject	1	2	3	4	5	6	7	8	9	10	Average
F.	14	11	24	15	9	4	8	4	12	7	12
C.P... ..	20	7	16	7	4	8	5	6	13	6	9
S.	4	8	12	3	10	15	9	9	7	4	8
B.P. ..	9	5	15	18	10	17	11	8	4	6	10
S.T. ..	0	0	8	4	12	4	10	5	10	11	6
L.B. ..	0	15	10	10	15	3	25	15	20	—	12
A.K. ..	17	9	11	18	15	25	12	4	16	23	15
N.	0	15	8	7	9	11	3	14	8	20	9·5
C.I.. ..	3	5	9	11	32	10	9	10	8	6	10
P.L. ..	12	15	8	16	12	20	5	9	20	14	13

Table giving errors of localization shown by ten subjects, each tested with radiated heat stimulation.

Errors measured in millimetres.

0 = no measurable error of localization.

— = stimulation not appreciated at all.

The most practicable source of heat was found to be supplied by a piece of platinum wire sealed in glass in such a way that only a small loop was left bare at one point. The wire was heated by the passage of an electric current so that the exposed loop became red-hot. The heat from other parts of the wire was taken up by the glass to some extent, and this was kept cool by some damp asbestos fibre wrapped round it. The free ends of the platinum loop were connected through a vulcanite holder to leads from the accumulators.

The stimulus was applied by approaching the glowing loop, by hand, to within about 1 mm. of the skin and withdrawing it at once. The error of localization was measured in the same way as for touch on similar photographs and diagrams and the results are given in Table V.

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NOTICES OF RECENT PUBLICATIONS.

The Evolution of the Nervous System in Invertebrates, Vertebrates and Man. By C. U. ARIËNS KAPPERS. Haarlem: Bohn. 1929. Pp. 335. Price 8.75 florins.

In his preface the author states that the purpose of his book is to give a general survey of the nervous system and to make his readers acquainted with its chief evolutionary principles, and no better description of its scope and use can be suggested. Starting with the nervous system of the invertebrates, which is dealt with only in sufficient detail to allow the reader to grasp the broad principles on which it is constructed, he gradually leads him through the lower vertebrate series to the primate brain, and finally, in a series of most interesting chapters, discusses the anthropology of the human brain, its characters in prehistoric man, and describes the chief morphological features of the brain in living races.

This treatment of the subject will appeal to the anthropologist, and indeed to all interested in the natural history of man, as well as to the student of medicine and neurology, and the simple and lucid presentation of the subject, the wealth of illustrations which supplement the descriptions, and finally the readable style in which the book has appeared, should ensure its popularity. It is not, however, merely a popular treatise thrown on the market to catch the eye of the casual reader. The author's eminence in this subject and his rigidly critical review of facts places it in a wholly different category. Anyone reading it through carefully will, for example, acquire a completer knowledge of the comparative anatomy of the vertebrate nervous system than he can obtain from any similar source, and will learn more of the mode of development of the cortex and basal ganglia than is easily available elsewhere.

For the anatomist this smaller volume cannot replace the author's now classical work on the comparative anatomy of the nervous system, but it deserves the attention of every neurologist, and especially of anthropologists who attempt to base observations and conclusions on scientific principles.

Anatomie du système nerveux. Par PAUL COSSA. Paris: Amédée Legrand. 1931. Pp. 400. Price 60 francs.

It is natural to expect that a textbook written by an anatomist acquainted with the needs of clinical investigation should be simpler and more useful to the student at least than the work of an academic anatomist who describes structures regardless of their clinical significance. Dr. Cossa is a clinician and has produced such a book suitable to the undergraduate student entering on a study of neurology. The main divisions of the nervous system are first described, and in the final chapters the chief systems of conduction tracts are dealt with separately. There are numerous illustrations, all simple drawings and many of them diagrams, on the whole adequate but rather crudely executed.

In view of its purpose it is naturally dogmatic and raises no doubts on many of the unsettled problems on which it touches, but unfortunately there are no references to which the reader can turn for further information, and few authorities are cited in support of statements made. The fact that French rather than Latin titles are given to most of the structures limits its value to English students.

Diagnostic des tumeurs cérébrales et épreuve de l'encéphalographie artérielle. Par EGAS MONIZ. Paris: Masson et Cie. 1931. Pp. 512. Price 100 francs.

The first third of this volume is devoted to a description and discussion of the symptoms of tumours of the brain, the remaining chapters to the use in diagnosis and localization of the method of arterial encephalography introduced by the author. This, as is now generally known, consists in the injection of a soluble substance opaque to X-rays into the internal carotid artery and the immediate exposure of a film in which the course of the larger cerebral vessels can be then seen. Sodium iodide is recommended in a 25 per cent. solution, and the author claims that if the precautions he advises are followed the injection entails little risk and few unpleasant complications. Fatal results followed immediately on injection in only two of his cases, both in patients with advanced arterial disease. The presence of a tumour can be recognized either by the presence of abnormal blood-vessels within it, or by the displacement of the arteries from their normal course.

There may be difficulties in the interpretation of the films, but these are fully discussed. The author's own experiences are illustrated by numerous figures which will be useful to others who wish to employ his method. Its value cannot be determined till independent observations are available, but Professor Monix, in this excellently written book, has at least furnished an interesting contribution to the literature of cerebral tumours.

Die Allgemeinerscheinungen der Hirngeschwülste. Von F. KEHRER. Leipzig: Georg Thieme. 1931. S. 116. Price M. 10.50.

This book contains two main chapters. In the first the ordinary and well-known signs and symptoms of cerebral tumours—as headaches, vertigo, vomiting, papillœdema, epileptiform attacks and psychical changes—are dealt with, and though little new is added to our knowledge the analysis and the discussions on the origin of some of those symptoms are undoubtedly important, as they are often accepted without question of their nature.

The second chapter bears the title of "A Group of New General Symptoms"; these include "Pain Reflexes" and "Pain Reactions," excited by mechanical stimulation of a nerve or of tissues in the peripheral distribution of a nerve. One striking feature of this sensitiveness of the tissues is that the patient is not conscious or aware of it. It is, therefore, an objective sign and is regarded by the author as evidence of irritability of protopathic sensation, and probably directly due to the increase of intracranial pressure. The importance claimed for these pain reactions is that they may make it possible to recognize the existence of a tumour before the classical signs of pressure appear, and in certain cases they may help in its localization.

The various "new signs" described by Kehrer must be studied in his book and controlled by independent clinical observations; till this is done their significance and importance cannot be determined. The book is certainly worth reading.

La myotonie atrophique; sa place entre la maladie de Thomsen et les myopathies. Par LUCIEN ROUQUÈS. Paris: Amédée Legrand. 1931. Pp. 229.

This excellent review of the clinical and pathological features of myotonia atrophica deserves the attention of all physicians interested in the muscular atrophies and in the hereditary diseases of the neuromuscular system. The clinical symptoms are fully described from the author's own observations and a review of the literature of this disease and of the related myopathies and myotonia congenita and their significance and relationships are discussed critically. Dr. Roquès had the opportunity of making a complete pathological study of one case only; this revealed no important differences from the eight cases in which autopsies had been already published, but it enabled him to re-examine certain points of interest and correlate the available pathological findings. A very extensive bibliography adds to the value of the volume.

The Commoner Nervous Diseases. By F. J. NATTRAS. Oxford University Press. London: H. Milford. 1931. Pp. 218. Price 12s. 6d.

This small book on the commoner diseases of the nervous system supplies a definite want in English medicine. It has been written chiefly for the general practitioner, but should also prove useful as an introduction to neurology for students.

The first chapter is an admirable exposition of the principles of diagnosis; it is illustrated by a series of diagrams and photographs, and written so clearly and concisely that even the least experienced can readily follow the routine of examination recommended by the author. Little reference is made to either the anatomy or the physiology of those parts of the nervous system involved by disease in explanation of the symptoms, and pathological anatomy and pathogenesis are in most cases neglected, but these scarcely come within the scope of the author's aim in producing this volume. The diseases and pathological conditions most commonly met with in practice are dealt with in separate chapters, considerable attention being given to their treatment.

Ueber Heilungsmechanismen in der Schizophrenie. Von MAX MÜLLER. S. 143. Berlin: S. Karger. 1930.

Regarding schizophrenia as an organic process characterized by onto- and phylo-genetic regression, Dr. Müller sets about the analysis of those reparative processes which spontaneously or in response to external influences tend towards restoration of the normal state of affective contact with the environment and adaptation to reality. He even includes as related mechanisms those in which the diffuse schizophrenic primary experiences are dominated or disposed of by higher psychic processes, and worked upon by logical thinking in the direction of systematized delusions. He uses mainly the phenomena observed during remissions, as well as descriptions of their experiences by the patients themselves.

The first part is concerned with the affective relations to the environment, especially as manifested towards the physician and in daily occupation. From the elaboration of psychotic experiences by intellectual and dynamic tendencies, the author passes to an inquiry into the formation of false beliefs, whether associated with insight or not, and the patient's subsequent refusal or inability to recapitulate the happenings of the acute illness. From his investigations, based on a rather small number of cases, the author is led to see opportunities of therapeutic intervention, but the indications are of the most general kind. Throughout the book there is evidence of wide and critical reading rather than of original thought or observation.

Frühsymptome geistiger Erkrankungen. von ERNST WITTERMANN. S. 32. Leipzig: Fischer. Price M.1.

This brochure is designed for the general practitioner, who is expected in Germany to have a rather fuller acquaintance with modern psychiatry than is usual in this country. The familiar early symptoms of mental disorder are set forth clearly and simply, with references to the work of Kretschmer, Gruhle and other recent writers. The organic reactions are dealt with best.

Ritual: Psycho-analytic Studies. By THEODOR REIK. With an Introduction by Sigmund Freud. Pp. 367. London: Hogarth Press. 1930. Price 21s.

This book has received the best of ancillary care; it is admirably translated and admirably set up. As a psycho-analytic study of the presuppositions and aims of religion it has much intrinsic value, and Dr. Reik explicitly repudiates any claim that his method is suitable for dealing with all the aspects of religious phenomena.

In a moderate and clear introduction he gives his reasons for selecting ritual still in use as the starting-point for an examination of religious problems.

The first section deals with couvade, which he regards as a landmark in cultural development, indicating the suppression of a fear of retaliation in favour of the more kindly and self-denying parental affections. The puberty rites of savages are then discussed with much learning and acuteness. The origins of the Kol Nidre renunciatory prayer are considered, and the strain of guilt running through all these ceremonies is related to primitive patricide. Finally, Dr. Reik offers an interpretation of the ritual significance of the ram's horn, with a discussion on the beginning of music and a supplement on the Moses of Michael Angelo (already treated by Freud) and the events on Sinai. To ethnologists who are prepared to accept psycho-analytic assumptions and methods of approach, this study will prove informative and stimulating; the more conservative will see in it daring conjecture, having the merit only of inner consistency.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

DECEMBER, 1931.

BRAIN.

PART 4, VOL. 54.

INTRACRANIAL AND SPINAL METASTASES IN GLIOMAS OF THE BRAIN.

BY HUGH CAIRNS[1] AND DOROTHY S. RUSSELL.[2]

(From the Bernhard Baron Institute of Pathology and Surgical Wards of the London Hospital.)

THE discovery of spinal metastases from a cerebral glioma in the first case described in this paper led us in 1928 to make a routine examination of the spinal cord in all cases of intracranial tumour, and as a result unexpected lesions of the spinal cord and its membranes have been brought to light. The frequency with which intracranial tumours are accompanied by tumours or other lesions in the spinal cord has in the past been greatly under-estimated. Our cases show clearly that no true indication of the frequency is given by clinical examination alone.

Lesions of the spinal cord that may be encountered at necropsy in cases of intracranial tumour are given in Table I. Most of these combinations have been encountered by us, and for the others references are given. The table could doubtless be amplified with increased experience. Examples of Groups 7, 8 and 9 provide interesting material illustrating the relationship of neurofibromas to meningiomas and gliomas. We are concerned here only with Groups 1 to 5. It has for some time been known that medulloblastoma of the vermis frequently gives spinal metastases or spreads directly into the spinal subarachnoid space. The fact that other varieties of glioma may give rise to similar metastases has not hitherto been emphasized. It seems, however, from the cases presently to be described that in special circumstances all varieties of glioma can give rise to metastases.

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[1] Working under a grant from the Rockefeller Foundation.
[2] Working under grants from the Medical Research Council.

TABLE I.—SPINAL LESIONS ASSOCIATED WITH INTRACRANIAL TUMOURS.

Brain	Spinal cord
1. Primary cerebellar glioma	Secondary glioma, by extension in continuity through foramen magnum
2. Primary cerebral glioma	Metastatic spinal glioma
3. Metastatic cerebral glioma (from glioma of retina)	Metastatic spinal glioma
4. Metastatic cerebral glioma	Primary spinal glioma [15]
5. Sarcomatosis of meninges	Sarcomatosis of meninges [17]
6. Primary cerebellar angeioma	Primary spinal angeioma [14]
7. Primary intracranial meningioma	Primary or ? metastatic spinal meningioma
8. Neurofibromatosis of roots of cranial nerves	Neurofibromatosis of roots of spinal nerves
9. Combinations of 7 and 8, with or without spinal glioma	
10. Primary melanomatosis	Primary melanomatosis [10]
11. Pituitary adenoma	Metastatic pituitary adenoma [1]
12. Metastatic carcinoma or sarcoma	Metastatic carcinoma or sarcoma
13. Primary intracranial tumour	Syringomyelia [13]

[1] A female, aged 25 (P.M. 153, 1931), who died in coma with hyperglycæmia, was found to have a large, very soft pituitary adenoma projecting into the base of the brain. During life it was observed that the cerebrospinal fluid contained cells of a peculiar type that were not identified. On naked-eye examination of the dorsal surface of the spinal cord a slight milky or rusty opacity of the pia arachnoid was observed in two places and there was a little reddish brown deposit at the extreme tip of the cauda equina. Microscopic examination of these areas revealed in the subarachnoid space among extravasated red corpuscles scattered, frequently multinucleated, cells which were identical with those composing the primary tumour. There was no indication of a multiplication of these cells *in situ*, nor did they appear to be in any way grafted on to the structures in their environment. No surgical procedure other than lumbar puncture had been done in this case.

HISTOLOGICAL METHODS.[1]

In the cases that follow, the material was fixed in 4 per cent. saline formaldehyde. Paraffin sections were stained with hæmatoxylin and eosin, iron hæmatoxylin and van Gieson's mixture, Weigert's fuchselin and neutral red, Laidlaw's silver method for reticulum, and, after treatment with Zenker's fluid, with Mallory's phosphotungstic acid hæmatoxylin. Frozen sections were stained by Herxheimer's method, and by Penfield's modification of Cajal's gold chloride-sublimate method, and of Hortega's silver carbonate methods for oligodendroglia and astrocytes. In addition the Marchi and Weigert Pal methods were employed in the examination of the cord in Case 2.

Where material was obtained by surgical operation, portions were fixed in Zenker's fluid and in formalin-ammonium-bromide as well as in formaldehyde, unless otherwise specified.

NOMENCLATURE.

Bailey and Cushing's classification [4] has been used in naming the different types of glioma encountered. In Case 1 the tumour differed histologically from any recognized type, and it has been decided temporarily to leave it unclassified.

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[1] The lists of tissues examined histologically in individual cases have been omitted to save space.

REPORT OF CASES.

Case 1.—*Glioma (unclassified) of third ventricle. Negative cerebellar exploration. Right transfrontal operation and biopsy. X-ray treatment. Death.*

History: Winifred B., aged 9, referred by Dr. Riddoch, was first seen on July 7, 1928, when she complained of attacks of right frontal and temporal headache and vomiting which had begun eight weeks before. These attacks lasted about a day, and in one of them she had been semiconscious for twenty-four hours and during that time had head retraction. Six weeks before admission she had come to her mother complaining of an unpleasant sensation in her right upper limb, and her mother observed that her left leg was shaking, and that she had some difficulty in speaking. This attack lasted about half an hour. From that time she began to suffer from almost continuous and often severe pain in the right knee and hip. Slight epistaxis had occurred from the right nostril at intervals during the illness. She had been quite steady in walking and there had been no disturbance of vision.

Examination: The patient was an intelligent and cheerful child, but during attacks of headache she became very irritable, and for several minutes at a time would show intense pallor of the face accompanied by slowing of the pulse-rate down to 60. Occasionally during these attacks she complained of feeling "hot all over." There was an engorged subcutaneous vein on the bridge of the nose. The fundi showed bilateral papillœdema (right, 1·5 D.; left, 2 D.). On one occasion during headache there was temporary complete left temporal hemianopia to 2/2000 and a relative left temporal scotoma to 5/2000 white, which in the light of subsequent events was probably caused by a temporary pressure on the right optic tract. The left pupil was slightly enlarged. There was slight weakness of the right side of the face and of the right lower limb. The reflexes on the right side were normal, but on the left side the lower abdominal reflex was diminished and the plantar reflex was extensor. She was slightly unsteady in walking when turning to the left, but showed no other sign of inco-ordination. There was generalized hypotonia. Passive movement of the right knee and hip was painful but not limited, and X-rays of this region showed no abnormality. Sudden twisting of the trunk produced sharp pain in the region of the right anterior superior iliac spine. In this region also there was an ill-defined area of cutaneous tenderness, but at that time no other change of sensibility was observed.

X-rays of the skull showed widening of the sutures, moderate enlargement of the sella turcica with erosion of all the clinoid processes and thinning of the dorsum sellæ. By lumbar puncture a slightly yellow cerebrospinal fluid was obtained which contained 0·5 per cent. of protein, and seven white cells per cubic millimetre.

Diagnosis.—It was clear that there was an intracranial tumour which probably occupied either the third or the fourth ventricle. The bilateral pyramidal signs and the attacks of pallor of the face associated with bradycardia were considered to favour a diagnosis of tumour of the third ventricle, but it was thought at that time that the pain in the right thigh and the changes in the cerebrospinal fluid were against this diagnosis and in favour of a tumour of the fourth ventricle. For these signs were regarded as being probably due to metastases in the spinal subarachnoid space, a complication well known to occur in cases of medulloblastoma, a glioma that is found almost exclusively (Cushing [7]) in the vermis of the cerebellum.

The patient was observed for a period of seventeen days, and during that time she developed double vision, and nystagmus at the extremes of lateral and upward movement of the eyes. An attack of coarse tremor of the right lower limb occurred which lasted fifteen minutes. At its height there appeared a fine tremor of the right upper limb, and a few involuntary movements of the muscles of the right side of the neck. She could move her limbs freely and her speech was not affected, and though she became quite pale she did not seem to be greatly distressed. During this attack the weakness of the right side of the face was accentuated.

The pain in the right lower limb persisted, but its area of maximum intensity shifted to the knee. She began to show a distinct limp when walking. Repeated examinations were made by Dr. Riddoch, Dr. Russell Brain and others to elicit more definite signs of spinal tumour, but the only signs obtained were slight cutaneous tenderness from the tenth thoracic to third lumbar segmental areas, diminution of all abdominal reflexes and of the right knee-jerk, limitation of extension of the lumbar part of the spinal column, and slight tenderness of the lower lumbar and upper sacral spinous processes.

On July 24 she began to have frequent and violent attacks of headache and vomiting, and during the night became delirious and unmanageable. It was decided to explore the fourth ventricle.

First operation, July 25, 1928: Ether anæsthesia. Cerebellar decompression was performed through the usual crossbow incision. The cerebellar tonsils were not displaced downwards and were so widely separated that by gentle retraction the whole of the lower half of the fourth ventricle could be seen. It was quite free from tumour. At an early stage of the operation both lateral ventricles were tapped and were found to be dilated. Subsequently, pressure on the cerebellum resulted in the escape of only a small quantity of fluid from the needles in the lateral ventricles. The fluid collected from the lateral ventricles, quite unlike that previously obtained by lumbar puncture, was colourless and contained only 0·08 per. cent. of protein and 1 white cell per cubic millimetre.

For two weeks after this operation the patient improved, but then she became drowsy and began to vomit once more. An attack occurred of clonic movements in the left lower limb. It was preceded by a sensation of falling and was accompanied by intense pallor of the face. It lasted two and one half minutes. Consciousness and speech were retained during the attack.

Second operation, August 16, 1928: Ether anæsthesia. In a further attempt to expose and remove the tumour, the region of the third ventricle was exposed by the right transfrontal route. On the outer aspect of the right optic nerve and right internal carotid artery a soft vascular process of tumour was found. This extended backwards towards the third ventricle, which felt unusually firm as if occupied by tumour. It was obviously impossible to remove the tumour completely and nothing was done beyond removing some fragments for histological examination. This showed a cellular glioma.

Subsequent course: The immediate post-operative course was uneventful except that the patient became incontinent of urine. As her condition was obviously desperate, an intensive X-ray treatment to the third ventricle was given seven days after operation. About fifteen hours later there was very great increase of intracranial pressure. The patient became unconscious and died on the following day. It is evident that the initial dose of X-rays should have been very much smaller, even though a cerebellar decompression had already been made.

Summary of Necropsy. (*P.M.* 386, 1928.)

Glioma (*unclassified*) *of third ventricle. Secondary glioma of spinal subarachnoid space. Operations: cerebellar decompression; right transfrontal exploration and partial removal of tumour.* Chronic focal descending nephritis. Petechial hæmorrhage in pericardium of margo obtusa. Slight anthracosis of lungs. Dilatation and post-mortem digestion of lower half of œsophagus. Mucous catarrh of stomach. Œdema and congestion of liver and spleen. Slight injection of synovial membrane of right acetabulum. Very slight atheroma of mitral valve and aortic commissure. Patent foramen ovale. A thin, well developed girl.

Macroscopic Examination.

Brain.—The brain was fixed *in situ* and removed eighteen hours after death. On sagittal section the lower anterior part of the third ventricle was found to be filled with a mass of tumour, measuring 3·2 by 2·3 by 2·0 cm., which projected up into the upper part of the ventricle between the anterior and middle commissures and elsewhere was attached to its walls. It lay immediately above the sella turcica, and the diaphragma sellæ presented a corresponding shallow cup-shaped depression. The tumour was firm, of the consistence of rubber, and its cut surface was grey or white and flecked with pin-point and linear red areas. It extended into the leptomeninges over the floor of the third ventricle and enclosed the optic chiasm and adjacent internal carotid arteries. A layer of grey tumour tissue, up to 0·3 cm. deep, covered the cerebral peduncles and spread backwards over the front of the pons and the adjacent cerebellum. The posterior communicating and posterior cerebral arteries, and the origins of the third to eighth cranial nerves on each side were obscured by this layer of tumour, but the basilar and vertebral arteries were superficial to it. The arachnoid membrane which covered them was white and opaque.

The arachnoidea over the convex surfaces of the cerebral hemispheres presented in places a faint milky-white appearance. The body and occipital horn of the left lateral ventricle showed a patchy, thin red deposit on their walls. The lateral ventricles were moderately dilated.

Spinal cord.—The posterior surface of the spinal cord presented a normal appearance down to the eighth cervical segment, but below that it was everywhere covered by a layer of greyish-white tumour tissue up to 0·25 cm. deep. There was slight opacity of the arachnoid membrane over the upper part of the cauda equina; below this the lower end of the spinal subarachnoid space was completely filled with a solid conical mass of tumour tissue, 1·3 cm. diameter. The anterior surface of the spinal cord for the most part retained its normal pattern, but showed a few patches of tumour tissue, up to 1·0 by 0·5 cm.; on the cauda equina there was a large white plaque of tumour, 2·0 by 1·2 cm., attached to the deep surface of the arachnoidea.

Microscopic Examination.

The primary tumour.—The tumour in the third ventricle is of somewhat loose texture and is subdivided by a wide-meshed network of collagen and small blood-vessels (fig. 1). The tumour cells lying in the spaces so formed lie parallel to one another in small bundles. In hæmatoxylin and eosin preparations the cytoplasm of these cells is difficult to observe; the groups of nuclei appear to be separated by a spongy network of fine eosinophil cytoplasmic threads. But in preparations stained with phosphotungstic acid hæmatoxylin it is clear that most of the cells are of tadpole shape and possess a simple long, tapering, finely-fibrillated process. In a group of cells the processes are given off in the same direction and stream in a leash towards a neighbouring blood-vessel or strand of collagen. In the upper half of the tumour and in a triangular zone adjacent to the leptomeninges covering its lower border, where the tissue appears to be best preserved, this palisading of the nuclei and the fibrillated character of the cell processes is very clear (fig. 2). Although the processes tend to radiate towards blood-vessels, there is no suggestion of the formation of foot-plates, nor is the arrangement definite enough to recall the perivascular "pseudo-rosettes"[1] of Bailey found in the more highly differentiated types of glioma, such as ependymomas and astroblastomas.

The nuclei are oval and of even size. They have a deeply-stained and well defined nuclear membrane and a fine chromatin net, with from one to four nucleoli and a number of small nodes of variable size. The nuclei do not appear as rich in chromatin as the nucleus of the medulloblast, as seen in typical medulloblastomas. No blepharoplasten are seen in the cytoplasm. Although nearly all the cells are of unipolar form, a few are less well differentiated; these show short blunt processes extending from one or both poles, or, more rarely, five or six short processes arranged in stellate fashion. The cells of the tumour are not impregnated by the gold chloride-sublimate method of Cajal. No giant cells and no mitotic figures are seen.

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[1] Much confusion exists over the use of the term "rosette" in connection with gliomas. Flexner [11] applied it to an arrangement of cells in neuro-epithelioma of the retina. In this the cells appear in section to be collected about a central lumen. Wright [22] again used the term to describe the arrangement seen in the so-called neuroblastoma, whereby the cells appear to be grouped in a circle the centre of which is occupied by their cytoplasmic processes. Bailey [1] and others give the name of "pseudo-rosette" to a perivascular arrangement of cells in which the cell processes are directed to the vessel wall, and also to the rosettes of Wright. They also broaden Flexner's definition of rosette to include cell formations in which the cytoplasmic border of the lumen is occupied by cilia and blepharoplasten. In this paper any terms used are qualified by the name of the author who first applied that term to that particular structure.

The reticulum is confined to the meninges and to the walls of the blood-vessels. In the periphery of the tumour, in one area, are numerous small hæmatoxyphil spheres of "calcification." The leptomeninges covering the lower border of the tumour are thickened by invading tumour cells and by a fibroblastic proliferation. The tumour cells here are less closely packed, and their form and disposition can be clearly seen.

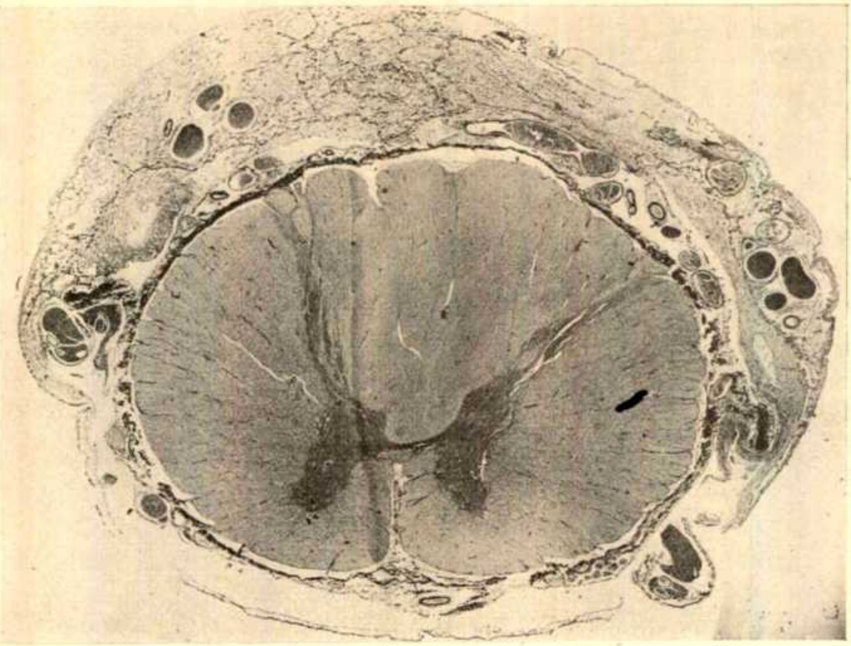

FIG. 3 (*Case* 1).—Spinal cord at eighth thoracic segment. The subarachnoid space over the dorsal and lateral aspects of the cord is filled with tumour. Phosphotungstic acid hæmatoxylin. × 9.

Intracranial extensions.—The leptomeninges of the medulla and adjacent cerebellum are extensively infiltrated with tumour cells of the same unipolar form, and the tumour extends into the sulci of the cerebellum. There is also slight infiltration of the leptomeninges of the left temporal cortex. There is no invasion of the nerve tissue or of the perivascular spaces of perforating vessels. Over the left Rolandic cortex there is slight fibrous thickening of the leptomeninges without infiltration by tumour. Beneath the ventricular ependyma there are a few recent perivascular hæmorrhages but no evidence of tumour.

Spinal metastases.—The subarachnoid space over the dorsal and lateral aspects of the cord is occupied by a crescentic mass, up to 3 mm. thick, of tumour cells and interlacing strands of collagen and reticulum (fig. 3). The reticulum is abundant, but there are occasional small islands of tumour cells that are free from reticulum. The tumour cells are identical with those found in the cranial meninges, and they do not infiltrate the substance of the cord. There is considerable focal degeneration and necrosis of these cells, associated with leucocytic and plasma cell infiltration.

Comment.—The tumour is a glioma of embryonic type. In its diffuse spread through the leptomeninges there is close macroscopic resemblance to medulloblastoma. It is, however, more differentiated than the typical medulloblastoma, and it contains very few cells that could be regarded as medulloblasts. Moreover, the absence of mitotic figures and of giant cells, the presence of nodules of calcification in the margin of the primary tumour, and the conspicuous production of collagen and reticulum in the infiltrated parts of the leptomeninges indicate a tumour of slower growth than medulloblastoma. The type of cell is a unipolar spongioblast with fibrillated cytoplasm (fig. 2). The absence of blepharoplasten differentiates it from an ependymal spongioblast, and the absence of vascular expansions distinguishes it from an astroblast.

From its histological appearances the tumour might justifiably be called a unipolar spongioblastoma. This name, however, has been given to a different kind of glioma that is composed of interlacing bundles of very long fibrillated uni- and bipolar cells, the processes of which are not directed towards vessels. The tumour reported in Case 1 is composed of a simpler and more primitive type of spongioblast than those found in the so-called spongioblastoma unipolare, and it is undoubtedly of a higher order of malignancy. The growth, therefore, cannot be called by any of the names used in Bailey and Cushing's classification, and for the present we do not propose to invent a name for it.

The case shows how previous beliefs about the occurrence of spinal metastases in cerebral gliomas may lead the observer astray in arriving at the correct localization of the primary tumour. The presence of severe pain in the right lower limb, of rigidity of the lower part of the spinal column, and of yellow spinal fluid of high protein content, indicated that there was a spinal tumour, presumably metastatic. This

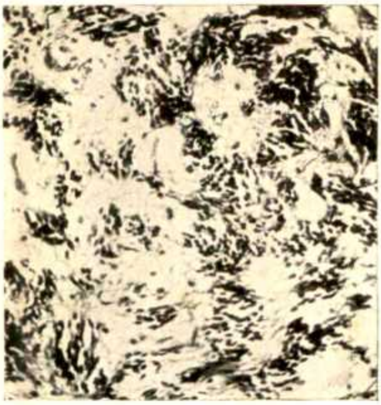

FIG. 1.

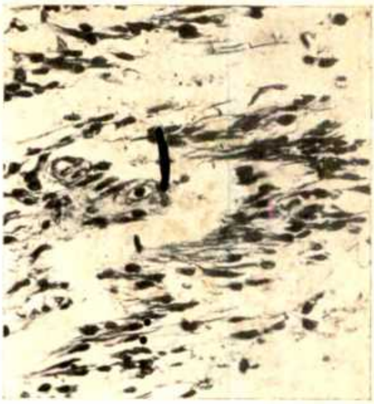

FIG. 2.

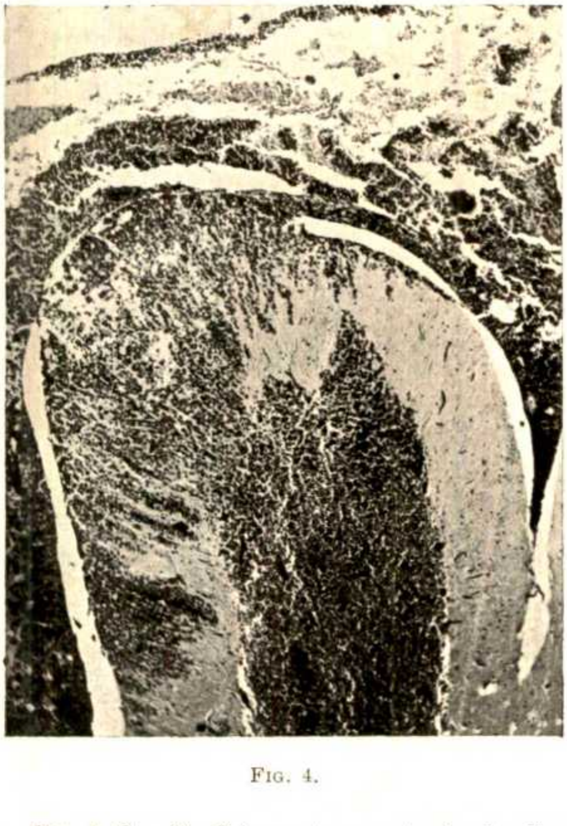

FIG. 4.

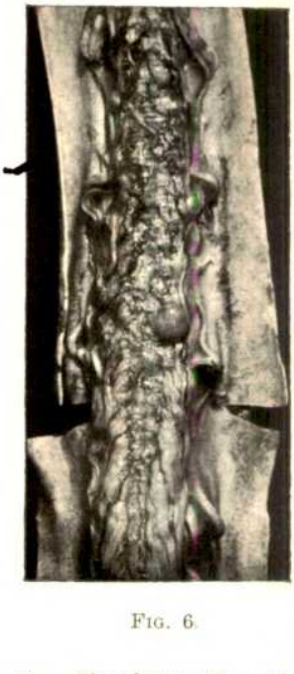

FIG. 6.

FIG. 1 (*Case* 1).—Primary tumour showing bundles of cells. Phosphotungstic acid hæmatoxylin. × 127.

FIG. 2 (*Case* 1).—Tumour in leptomeninges showing fibrillated unipolar cells with processes directed towards vessels. Phosphotungstic acid hæmatoxylin. × 222.

FIG. 4 (*Case* 2).—Invasion of folium of cerebellum by tumour cells from adjacent leptomeninges. Phosphotungstic acid hæmatoxylin. × 75.

FIG. 6 (*Case* 3).—Posterior surface of lower portion of spinal cord showing metastatic nodule on third lumbar segment.

To illustrate paper by Hugh Cairns and Dorothy S. Russell

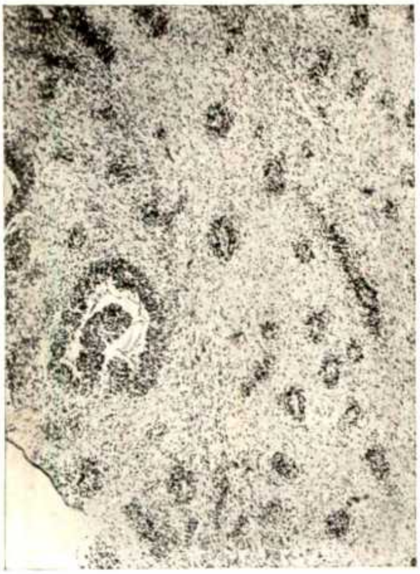

FIG. 7.

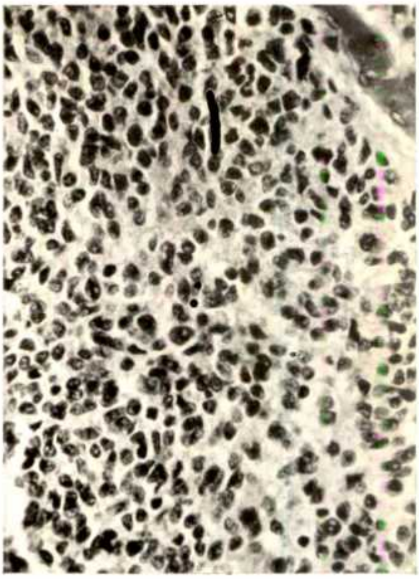

FIG. 8.

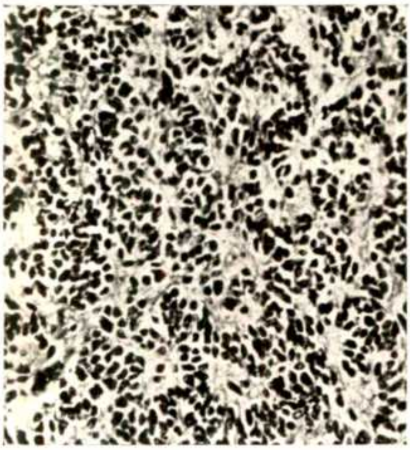

FIG. 10.

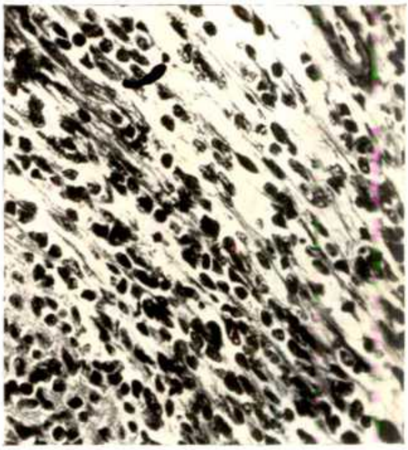

FIG. 11.

FIG. 7 (*Case* 3).—Wall of left lateral ventricle showing infiltration. Hæmatoxylin and eosin. × 42.

FIG. 8 (*Case* 4).—Medulloblastoma. The primary tumour. Hæmatoxylin and eosin. × 263.

FIG. 10 (*Case* 5).—Medulloblastoma. Primary tumour showing general arrangement of cells. Phosphotungstic acid hæmatoxylin. × 195.

FIG. 11 (*Case* 5).—Primary tumour showing fibrillated spindle cells. Phosphotungstic acid hæmatoxylin. × 380.

To illustrate paper by Hugh Cairns and Dorothy S. Russell.

PLATE XIV.

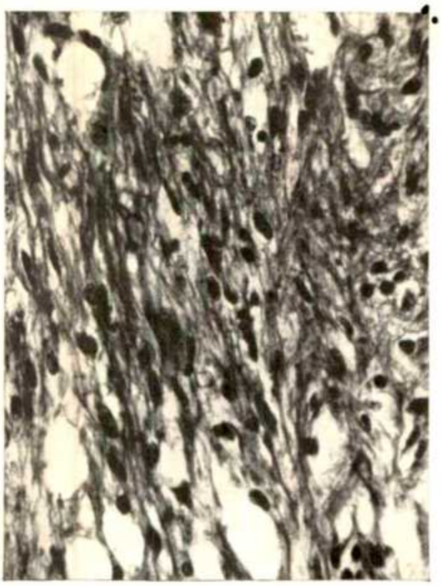

FIG. 12.

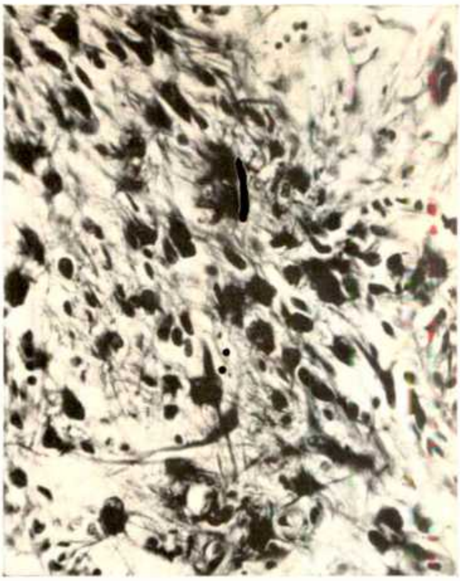

FIG. 14.

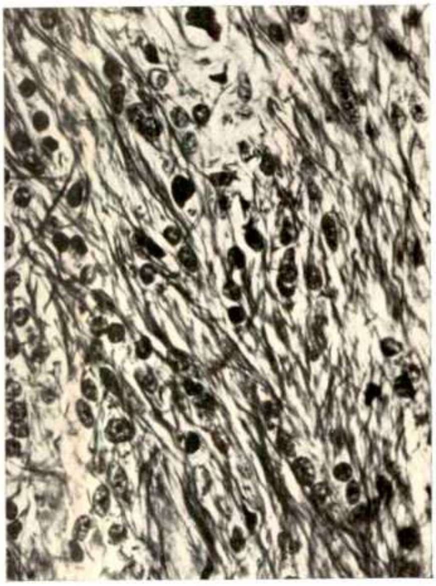

FIG. 15.

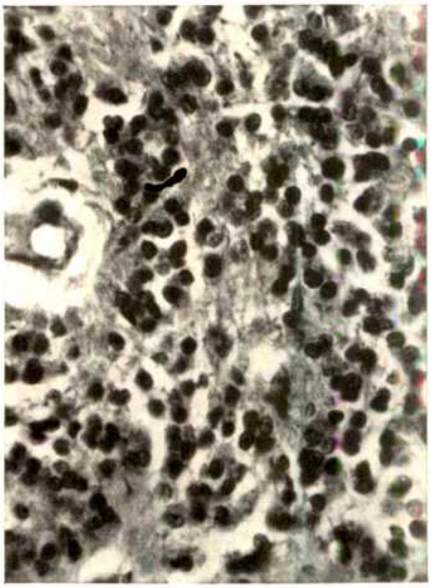

FIG. 16.

FIG. 12 (*Case* 6).—Glioblastoma multiforme. Tumour in genu of corpus callosum. Spindle cells with abundantly fibrillated cytoplasm are seen. Phosphotungstic acid hæmatoxylin. × 300.

FIG. 14 (*Case* 6).—Metastatic nodule attached to root in cauda equina. Numerous astrocytes and a few bipolar cells are demonstrated. Silver carbonate method for astrocytes. × 300.

Fig. 15 (*Case* 8).—Ependymoma. Primary tumour showing fibrillar area. The cells are elongated and contain numerous neuroglial fibrils. In several places blepharoplasts are seen in the cytoplasm close to the nucleus. Phosphotungstic acid hæmatoxylin. × 281.

FIG. 16 (*Case* 8).—Ependymoma. Primary tumour showing cellular area. The cells have a tendency to arrange themselves in groups round a central lumen. Phosphotungstic acid hæmatoxylin. × 281.

To illustrate paper by Hugh Cairns and Dorothy S. Russell.

was regarded as evidence in favour of cerebellar medulloblastoma, the only variety of glioma, with the exception of glioma of the retina, that has hitherto been recognized as a common source of metastases in the spinal subarachnoid space. Thus, in the presence of signs highly suggestive of a lesion of the third ventricle, we were led to explore first the cerebellum. It is remarkable that such extensive spinal metastases should produce such slight sensory and motor changes in the lower limbs.

This case clearly indicated the desirability of routine examination of the spinal cord at necropsy in all cases of cerebral glioma, and further examples of unsuspected spinal metastases were soon disclosed. The case reports that follow show that spinal metastases are not limited to the very malignant types of glioma, but may occur in almost all varieties.

NEURO-EPITHELIOMA.

Case 2.—Glioma (neuro-epithelioma) of left eye. Enucleation of eyeball. Local recurrence, treated by radium. Massive invasion of central nervous system by tumour. Death.

History: Arthur L., aged 3 years, was first admitted to the London Hospital under Mr. Goulden, on November 4, 1929, with the history that his mother had noticed one week before that his left eye was red and watery. The child had also suffered for some time from difficulty in breathing through the nose and from nasal discharge.

Examination: The lids of the left eye were swollen and there was considerable conjunctival and ciliary injection. The cornea was very cloudy though not ulcerated, and it had no reflex. The anterior chamber was partially filled with exudate and the iris was discoloured. The tension of the eye was normal. The child was rather drowsy, but general examination showed no other signs.

For one month the eye was treated with atropine and baths. The condition failed to improve and chemosis of the conjunctiva gradually developed. Therefore, on December 5, 1929, the left eye was excised.

Macroscopic Examination.

(Report of naked-eye appearances and histological preparations kindly provided by Mr. H. B. Stallard, of the Royal Ophthalmic Hospital, Moorfields.) The circumcorneal blood-vessels were injected. There was a hypopyon and the filtration angle of the anterior chamber was occluded by peripheral synechiæ. The lens was swollen and vacuolated. A yellowish white tumour with granular surface and soft friable consistency appeared to arise from the retina, which was almost entirely destroyed, and extended into the vitreous chamber. The choroid and optic disc were infiltrated and fragments of the tumour lay among the ciliary processes. There were several small areas which gave a gritty sensation when the eye was divided. There was no macroscopic evidence of extra-ocular extension. The specimen was fixed in Zenker's fluid. After vertical division the globe was decalcified and embedded in celloidin.

Microscopic Examination.

In a median antero-posterior section, stained by hæmatoxylin and eosin, the posterior chamber is occupied by closely packed masses of tumour cells, which do not appear to be arranged in any special manner. Most of them are in various stages of degeneration and there are large anastomosing areas of necrosis, many of which contain neutrophil leucocytes. In the borders of such areas are occasional small deposits of amorphous, deeply hæmatoxyphil substance suggestive of calcium. The whole of the retina is replaced by tumour. Along one side of the globe the choroid is replaced at intervals by tumour cells and, on the same side, there is infiltration of the anterior layer of the iris and the lateral angle of the anterior chamber by tumour. The anterior chamber is filled with degenerating tumour cells and neutrophil leucocytes. The peripheral parts of the retina, which are not connected with the main mass in the posterior chamber, alone show a conspicuous arrangement of the tumour cells in rosettes of Flexner. These rosettes are hollow spheres, as can be seen in thicker parts of the section. In thinner parts they appear as a ring of cells, the nuclei of which lie at variable distances from the lumen. The nuclei are round, oval or pyriform; the narrow end of the pyriform examples is directed towards the lumen. They have a thick deeply-stained nuclear membrane and a thinner chromatin net beset with many fine dust-like nodes. There are no nucleoli. There is no demonstrable cytoplasm on the side of the nucleus remote from the lumen, but on the side towards the lumen there is a lightly eosinophil extension which ends in a more deeply eosinophil membrane. This membrane is slightly fuchsinophil when stained with van Gieson's mixture and appears pinkish-purple or purple in Mallory's phosphotungstic acid hæmatoxylin. Adjacent to the membrane on either side is a variable number of minute particles of inconstant size with similar staining properties, and occasionally small rounded bosses are seen that appear to be cytoplasmic protrusions beyond the membrane into the lumen. The lumen itself is frequently occupied by free tumour cells or by spheres that appear to be cytoplasmic detritus. There is no evidence of either cilia or blepharoplasten in the cells. Mitotic figures are very frequent.

Subsequent course: The child was discharged from hospital on December 15, 1929. In the following April he became irritable and swelling of the left eyelids recurred. In May it was found that there was a firm mass filling the whole of the left orbit and displacing the conjunctiva forwards. This was treated for six days by radon seeds and radium needles (total dosage, 1,728 millicurie hours). The eyelids became very swollen and sloughs discharged from the socket. In June, 1930, the child developed rubella and scarlet fever and was sent to an infirmary. He was admitted to the London Hospital once more in August in a wasted condition and suffering from loss of appetite.

There was now a large, irregular, firm red mass of tumour projecting forwards between the left eyelids, and from it came an offensive purulent discharge. On August 28, 1930, radium needles and radon seeds were again inserted into the tumour mass (12 mc. radium for five days, 6 mc. radon left *in situ*). There was severe vomiting for forty-eight hours. His condition then improved for a short time but he was still drowsy, and in the middle of September he became lethargic and began to vomit. Weakness of the right side of the face, increased tendon-jerks on the right side, and an extensor plantar reflex on both sides were observed. Two weeks later a projection of the right retina appeared below and to the outer side of the right optic disc, suggesting the presence of tumour behind. Vision of the right eye gradually failed, and in November the eye began to project forwards and its cornea became hazy. Vomiting occurred frequently, and the child became greatly wasted and finally died on November 28, 1930, almost twelve months after the primary tumour had been removed.

Summary of Necropsy. (*P.M.* 522, 1930)

Marasmus. Gliomatosis of ventricles and of leptomeninges of brain and spinal cord. Primary glioma of left retina. Old operation: excision of left eyeball. Clear fluid in both middle ears. Slight œdema of myocardium. Atheroma of aortic cusp of mitral valve. Slight congestion and considerable emphysema of lungs. Œdema and considerable congestion of liver, spleen and kidneys. Congestion and mucous catarrh of stomach. Greatly wasted child.

Macroscopic Examination.

Orbits.—The left eyelids were glued together by a glistening brown membrane. In the centre of the left orbit there was a conical abscess cavity (1·8 by 0·7 cm.), the apex of which was directed backwards. It contained four radon seeds and thick brownish yellow pus. Its walls were composed of firm greyish white tissue, in some parts stained an orange colour. There was to the naked eye no evidence of tumour in the soft tissues of the right orbit, either in the orbital part of the optic nerve or in the right eyeball.

Brain.—The leptomeninges at the base of the brain were everywhere occupied by a milky-white deposit of finely granular appearance, which contained flattened areas (0·1 to 0·2 cm. in diameter) of greater opacity. This infiltration was most evident on the inferior surface of the cerebellum, in the cisterna basalis, on the orbital surface of the right frontal lobe, and on the inferior surfaces of both temporal lobes. In these places the sulci were conspicuously infiltrated with white deposits. The infiltration extended on to the superior surface of the cerebellum, the opposing surfaces of the great longitudinal fissure, and also on the convexities of the cerebral hemispheres in the form of discrete miliary deposits (0·1 cm. in diameter).

The optic chiasm and left optic nerve were replaced by a rounded, soft, friable greyish yellow mass (2·3 by 2·5 by 2·5 cm.). The proximal part of the right optic nerve (0·8 cm. in diameter) was also thickened by greyish white infiltration. The proximal parts of the third and sixth cranial nerves on each side were occupied by greyish white nodular masses (up to 0·7 cm. in diameter), and the remaining cranial nerves were all embedded in a continuous mass of similar tissue (2·3 by 1·5 by 1·0 cm.) on each side of the pons and medulla oblongata. The pons was laterally compressed by these masses.

The floor of the third ventricle was replaced by a flocculent mass of growth continuous with the mass in the chiasmal region. The tela choroidea was covered with a gelatinous grey sheet of opaque tumour tissue continuous with the tumour in the leptomeninges of the great transverse fissure. The walls of both lateral ventricles and the fourth ventricle and the lateral walls of the third ventricle were studded with glistening grey nodules (up to 0·3 cm. in diameter). The choroid plexuses of the lateral ventricles appeared to be normal, except that there were a few nodules of tumour on the right choroid plexus at the foramen of Monro. There was moderate internal hydrocephalus.

Spinal cord.—The spinal subarachnoid space was everywhere distended with tumour tissue (up to 2·3 from side to side and 1·8 cm. from before backwards), appearing on section as homogeneous glistening greyish white growth enclosing the spinal cord. In the lower thoracic region the pattern of grey and white matter was not greatly disturbed by infiltration, but in the second thoracic segment the cord appeared on section as a central small trifoliate area, the margins of which were greatly eroded by infiltration. At the level of exit of the first lumbar nerves the cord (0·7 by 0·5 cm.) appeared to be extensively infiltrated by tumour.

Microscopic Examination.

Orbital extensions.—In the longitudinal section of the soft tissues of the left orbit a chronic abscess occupies the anterior half of the mass. The abscess cavity has a broad marginal zone of necrotic tissue beyond which is a stout layer of collagen infiltrated with numerous plasma cells and other cells that appear to be degenerating tumour cells. Amongst these are intra- and extracellular masses of golden brown pigment which give a positive reaction for iron. The orbital muscles are bound to this dense wall of collagen. There is atrophy and degeneration of the muscle fibres. Immediately behind the abscess is a triangular mass of tumour cells, interspersed with stout strands of collagen and enclosed laterally by collagen. There are irregular areas of necrosis amongst these tumour cells.

In a longitudinal section of the right eye the tumour-cells are present along the course of the ophthalmic artery in the optic nerve, and a few cells lie around the small blood-vessels in the superficial layer of nerve fibres in the optic cup. Tumour cells lie in the sheath of the optic nerve between the collagen and the nerve fibres. They extend peripherally as far as the choroidal coat. There is no evidence in the retina of a second primary tumour or of invasion by tumour.

Intracranial extensions.—The cells composing the intracranial extensions are small round cells of the same kind as those in the retinal tumour. They are clumped together without any suggestion of rosette formation. In sections stained with phosphotungstic acid hæmatoxylin there is no suggestion of blepharoplasten or fibrils in the scanty cytoplasm of these cells. The rounded mass replacing the optic chiasm is composed of cells that are very loosely aggregated in the meshes of a poorly-vascularized scanty stroma. Much of the tissue has crumbled away and been lost in the process of embedding. There is extensive degeneration and necrosis of the cells, but in the neighbourhood of the vessels they are better preserved.

The inner border of the collagen sheath surrounding the right optic nerve is densely infiltrated with tumour cells. The cells encroach inwards between the bundles of nerve fibres and also infiltrate the nerve bundles themselves, especially at the edge of the section. A small area in the centre of the optic nerve is free from tumour.

There is extensive infiltration of the cerebral and cerebellar leptomeninges with tumour cells without apparent increase of reticulum. The cells also invade the cortex by way of the perforating vessels, forming stout cuffs both in the perivascular sheath and outside the sheath in the brain substance. A few rounded masses of tumour cells are also present in the cortex without any apparent relation to blood-vessels. This appearance may be the result of tangential section of perivascular masses. In the cerebellum columns of invading cells are seen in the molecular layer (fig. 4) which expand in a flask-like fashion on reaching the granular layer to extend around and deep to the Purkinje cells.

In the roof of the left lateral ventricle there is a thick irregular subependymal zone of closely packed tumour cells. The ependyma is raised into bosses by this infiltration and is missing at many points on their convexities. In a few places there is no subependymal infiltration. The tissue is moderately vascular and there are relatively few islands of necrosis. Reticulum is confined to the vessels.

Spinal extensions.—There is enormous distension of the subarachnoid space by densely packed tumour cells, especially in the lower thoracic cord. The blood-supply of these cells is scanty, and foci of degeneration and necrosis are conspicuous. The cells surround and invade the nerve roots, and there is extensive invasion and destruction of the cord itself in the form of large bays that encroach on the white matter. There is also, besides this direct extension inwards, a conspicuous infiltration of the perivascular spaces of the perforating arterioles forming thick cuffs. The cells are also present to a less extent in sleeves outside the pial invagination around these vessels. They are indistinguishable from the cells of the primary retinal tumour. There is severe degeneration of the anterior horn cells with much loss of Nissl substance and disappearance of their nuclei.

Comment.—In this case there was a primary tumour of the left retina which recurred in the left orbit after removal of the eyeball and spread profusely to the optic chiasm and right optic nerve and to the leptomeninges of the brain and cord. It invaded the floor of the third ventricle and extended on the walls of all the ventricles. It also spread into the ventricles by way of the great transverse fissure and tela choroidea. The presence of well-developed rosettes of Flexner [11] in the primary tumour identifies it as a neuro-epithelioma of the retina, as defined and described by that author. The histological appearances agree closely with those described in his case. In our case the tumour cells infiltrating the brain, cord and leptomeninges did not form rosettes and were indistinguishable from medulloblasts.

In their structure, their high degree of malignancy and method of spread gliomas of the retina are very similar to medulloblastomas of the vermis and they are probably closely allied tumours. It has been suggested that the presence of rosettes in glioma of the retina betokens a lessened degree of malignancy as compared with tumours in which such formations are absent. The malignancy of this case, in which rosettes were present, was of such degree that it is doubtful whether this contention is correct.

MEDULLOBLASTOMA.

Case 3.—Glioma (medulloblastoma) of cerebellum. Partial removal by operation. X-ray treatment. Temporary improvement. Sudden death after interstitial radon treatment.

History: R.H., a boot maker, aged 19 years, was admitted to the London Hospital on August 2, 1928, under the care of Dr. Cecil Wall. Apart from illnesses in childhood, he had been perfectly well until three months before admission, when he began to "talk through his nose" and to suffer from a heavy feeling in the head. The trouble with talking gradually increased, so that he had to pause for breath after each word. He was at first treated for nasal catarrh and deviation of the nasal septum, but four weeks before admission he began in the afternoons to have attacks of giddiness, followed by frontal headache and vomiting. In the attacks he had a sensation of falling backwards, and he would stagger and occasionally fall. At other times his gait was steady. The headaches became worse, so that one week before admission he could no longer work. He began to suffer from weakness of the right hand, and this was followed by occasional attacks of numbness of the right upper limb which lasted half an hour. From the onset of the illness he had occasionally seen distant objects as double, but his sight was not otherwise affected until a few days before admission, when it became dim during an attack of headache, and he saw lights and stars.

His speech became so bad that people could not understand what he was saying, and finally, after an intense attack of headache and vomiting, he passed into a state of stupor. On the following day he rallied partially and was then brought to the London Hospital. A lumbar puncture was done on the day of admission and 15 c.c. of clear cerebrospinal fluid, under greatly increased tension, were withdrawn (protein, 0·017 per cent.; no white cells). Subsequently he was given rectal infusions of magnesium sulphate. For a week after admission he felt much better, though he continued to have occasional attacks of headache and vomiting. Later, the attacks of headache became very severe and extended to the back of the neck. In addition, he began to have pain in the right side of the face. He was transferred to the surgical wards on August 11, 1928. At no time during the illness was there any difficulty in swallowing or regurgitation of fluids through the nose.

Examination: The patient was in great pain and was at times drowsy. He yawned frequently. The other positive findings were pronounced dysarthria; generalized tenderness of the skull, greatest in the suboccipital region, and of the back of the neck; bilateral papillœdema (2·5 diopters); venous engorgement and swelling of upper eyelids; bilateral ptosis; weakness of right external rectus; slight weakness of lower part of face on the left side; occasional relative deafness of right ear; generalized hypotonia; slight dysmetria, ataxia and dysdiadokokinesis of all four limbs; diminution of all tendon-jerks, especially the knee-jerks; slight enlargement of the sella turcica and erosion of the clinoid processes. No objective changes were found to correspond with the numbness of the right arm and the pain in the right side of the face. Examination of the tongue and palate showed no defect of movement, and fluids were swallowed without any trouble. There was no nystagmus. During the three days before operation the pulse-rate slowed from 70 to 46, and the respirations became slow, periodic and sighing in character.

Operation, August 14, 1928: Under local anæsthesia, with the addition of morphia, $\frac{1}{6}$ gr., the cerebellum was exposed by the usual crossbow incision. When the dura was opened the cerebellum bulged greatly, in spite of the fact that the intracranial tension had been previously reduced by tapping the occipital horns of the lateral ventricles. Both tonsils were displaced through the foramen magnum, and the arch of the atlas was therefore removed. The tonsils were widely separated, but no tumour was found in the region of the medulla or calamus scriptorius. A median vertical incision was now made in the vermis, and at a depth of 4 cm. an ill-defined, soft, grey tumour was encountered, high up under the tentorium. After fragments had been removed for section (S.D. 1940, 1928), the tumour was sucked out, but, owing to the condition of the patient and the fact that the tumour was in a relatively inaccessible part of the vermis, removal was not complete.

Post-operative course.—After operation there was complete relief from headache, vomiting and vertigo, and articulation improved. Papillœdema subsided and visual acuity was $\frac{6}{9}$ in each eye. On discharge from hospital thirty-one days after operation he could walk unaided, but his gait was still ataxic. He returned to work.

X-ray treatment was begun by Dr. Vilvandré in September, 1928, but the patient was not regular in attendance for treatments. In February, 1929, he began to suffer once more from headache, and his walking and the movements of his left hand became more unsteady. After each X-ray treatment he experienced temporary relief, but ataxia of the left hand steadily increased and prevented him from working. In June, 1929, the relief after X-rays was much less than it had been earlier in the year. On July 17, 1929, he was re-admitted to hospital for radium treatment. He was at this time drowsy, irritable, and incontinent of urine and fæces. Papillœdema had recurred (4-5 D.) with the formation of retinal hæmorrhages, and visual acuity had diminished. There was left hemiparesis of moderate degree and almost complete right facial paralysis. A careful examination was made for clinical evidence of spinal metastases, but beyond doubtful analgesia up to the sixth thoracic segmental level on the right side there was nothing that could be clearly attributed to a lesion of the spinal cord. On July 18, radon seeds containing 11 millicuries were inserted into the tumour in the region of cerebellar vermis by trocar and cannula. Two hours later the patient suddenly stopped breathing and died.

Summary of Necropsy. (*P.M.* 275, 1929.)

Hæmorrhage into glioma (medulloblastoma) of cerebellum. Operation: old cerebellar decompression; recent insertion of radon. Bilateral focal fibrous pleurisy. No tuberculous nodules in lungs or in bronchial lymph glands. Healed appendicitis; fibrous stricture with fibrosis and muscular hypertrophy of appendix. Uniform colloidal hypertrophy of thyroid gland. Congestion of liver, kidneys, and mucosa of stomach. Foramen ovale patent. Very slight atheroma of descending thoracic and abdominal aorta, and of bifurcation of carotid arteries. Polypous adenoma (0·6 cm. in diameter) in pelvic colon. Meckel's diverticulum (4·5 by 1·6 cm.) situated 106 cm. above cæcum. A wasted lad.

Macroscopic Examination.

Brain.— The brain was fixed *in situ* nineteen hours after death. A very large tumour (8·0 by 7·5 by 4·5 cm.) occupied the greater part of the cerebellum. In its posterior part about 2 to 3 drm. of blood-clot surrounded radon seeds. This hæmorrhage presumably followed the insertion of radon and was the immediate cause of death. Apart from the area of hæmorrhage the cut surface of the tumour was soft, pinkish white and faintly granular. The tumour involved the upper surface of the vermis and left lateral cerebellar lobe, and the roof of the fourth ventricle. It extended more to the left than the right and invaded the tentorium on the left. On each side the anterior surface of the lateral cerebellar lobe was displaced into the internal auditory meatus. The pons and medulla oblongata were flattened against the basi-sphenoid and basi-occiput. The upper part of the pons was displaced to the right, while the lower part of the medulla oblongata and the adjacent cervical spine were displaced to the left.

The aqueduct of Sylvius was dilated (0·35 cm. in diameter). The third ventricle, however, was not dilated; its walls were thrown into folds by a layer of tumour tissue, its floor was slightly thickened (0·15 cm.), and anteriorly its right lateral wall presented a nodule of tumour (1·5 by 1·0 cm.) which projected up to 0·4 cm. into the lumen of the ventricle (fig. 5). Both lateral ventricles were small and appeared everywhere to be lined with tumour tissue, which in some places produced longitudinal corrugations and in others nodular projections (up to 0·8 cm. in diameter) (fig. 5). In places the tumour lining the ventricles had invaded the adjacent brain; the fornix was almost completely replaced by grey granular growth, and the lower surface of the corpus callosum was invaded to a depth of 0·7 cm. The left hippocampal gyrus contained an extension of tumour from the left temporal horn that measured 2·6 by 1·8 cm. The anterior part of the pineal gland (0·8 by 0·6 cm. in sagittal section) was replaced by a nodule of granular white tumour (0·5 by 0·3 cm.). The surfaces of the cerebral hemispheres appeared to be free from metastases.

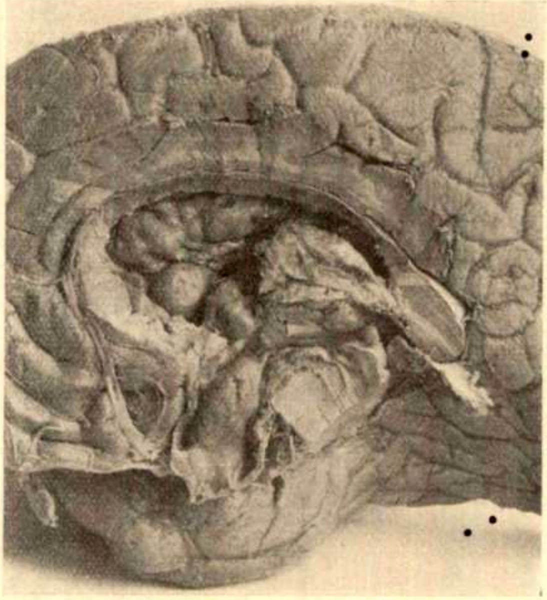

FIG. 5 (*Case* 3).—Right lateral and third ventricles with corpus callosum cut away to show growth in their walls.

Spinal cord.—There was a brownish white hemispherical nodule (0·6 cm. in diameter) on the right side of the posterior surface of the third lumbar segment (fig. 6). On the arachnoid over the posterior surface of the fourth thoracic segment there was a small grey nodule (0·2 cm. in diameter). Elsewhere the cord and its membranes appeared to be free of metastases.

Microscopic Examination.

The primary tumour.—The borders of the tumour in the cerebellum are ill-defined and the neighbouring cerebellar folia, the roof of the fourth ventricle and tentorium cerebelli are invaded by the growth. The tumour is of a richly cellular nature. The cells are closely packed together, especially about the blood-vessels. In parts distant from the vessels there are often small poorly-defined areas of degeneration and necrosis which are sometimes occupied by collections of neutrophil leucocytes. There are also small irregular cystic spaces containing rounded masses of homogeneous eosinophil substance. In the tentorium the tumour cells often lie in parallel rows between collagen strands or in rounded masses, the centres of which are less densely cellular than the periphery.

The individual cells have round or oval nuclei with a deeply-stained fairly thick nuclear membrane and a fine chromatin net beset with a few nodes of variable size. There are one or two conspicuous nucleoli in the majority of the nuclei. The cytoplasm is eosinophil and very scanty; it appears fluffy and is not prolonged into definite processes. In preparations stained with phosphotungstic acid hæmatoxylin there is no evidence of fibrils or of blepharoplasten. The cells are refractory to the gold chloride sublimate method of Cajal.

The cerebral extensions.—The walls of the third and lateral ventricles, including the ventral part of the fornix, are diffusely infiltrated with cells of the same kind as those in the primary tumour (fig. 7). The cells are chiefly collected in dense zones beneath the ependyma and round the blood-vessels in the deeper tissues. In the third ventricle the infiltration extends down to and involves the leptomeninges covering the floor. The ependyma is intact in some places and in many others is replaced by masses of tumour cells. In the descending horn of the left lateral ventricle fissures lead from the cavity into the adjacent infiltrated tissue. There is considerable degeneration of the cells that are remote from blood-vessels and numerous fat granule cells lie amongst them. The majority of blood-vessels that are surrounded by tumour cells appear normal, but in others the walls are thickened by an increase in the number of endothelial cells, and in certain of these the endothelial cells appear to be mixed with tumour cells which have spread inwards by direct extension across the perivascular space. The infiltration is especially dense in the left hippocampal gyrus, and in one part the tumour cells extend outwards as far as the surface of the brain, occasionally breaking through into the leptomeninges. The anterior half of the pineal body is densely infiltrated with tumour cells, but the rest of the gland appears normal. There is no evidence of tumour in the leptomeninges of other parts of the cerebral hemispheres, or in the portions of the optic tract examined.

The spinal metastases.—The fifth cervical segment is free from tumour. The left dorsal root of the fourth thoracic segment and both dorsal roots of the third lumbar segment are surrounded by a circumscribed lenticular mass of tumour cells occupying the subarachnoid space close to the exits of these roots from the spinal cord. Of these the mass on the right third lumbar root is the largest. The cells are arranged in round clumps or in columns along the collagen strands that form the stroma of these metastases. There is slight invasion of the marginal glia of the cord by tumour cells at the medial extremity of the largest metastasis only.

The fundi.—There is papillœdema but no invasion by the tumour cells.

Comment.—This glioma is, histologically, a typical medulloblastoma. The ventricular method of spread in this instance offers a striking contrast to the distribution of metastases observed in the next case to be described. In this connection it is to be noted that when first disclosed at operation the tumour was limited to the upper part of the vermis and did not extend into the cisterna magna. This fact doubtless influenced the method of spread.

Case 4.—Glioma (medulloblastoma) of cerebellum invading pons and medulla oblongata. Numerous cerebral and spinal metastases. Cerebellar decompression and partial removal of tumour. Early fatality.

History: Bernard B., aged 5½, referred by Professor Ellis, was first seen on June 30, 1930. Six months before this he began to suffer from slight headaches and drowsiness, and a few weeks later from projectile vomiting, especially in the mornings. He rapidly lost weight and his legs gave way at times when he was walking. Five weeks before admission he seemed very weak and was confined to bed; and at this time also he began to have difficulty in micturition, which later changed to incontinence. On two occasions, about three weeks before admission, he appears to have had attacks of extensor rigidity. Attacks of coughing occurred frequently. He became increasingly languid, but the headaches were never severe and they disappeared completely one month before admission.

Examination: The boy was intelligent but irritable and lethargic, and was very wasted. His head was slightly enlarged (circumference 51·6 cm.) and there was spasm of the muscles of the right side of the back of the neck. There was also considerable hyperextension and rigidity of the neck. His face and trunk were persistently rotated towards the right and he strongly objected to being placed on his left side. Though his parents had not noticed anything wrong with his vision, the boy was almost blind; he could not count fingers beyond 2 ft. with his right eye and had perception of light only in the left eye. There was bilateral papillœdema (right, 4·5 D; left, 6 D) with secondary atrophy and perivascular exudate. The upper eyelids were engorged and both eyeballs were rather prominent. There was persistent conjugate deviation of the eyes to the right, together with almost complete loss of voluntary conjugate movement to the left. At the extremes of his lateral ocular movements there was coarse ill-sustained nystagmus. Upward movement of the right eye was slightly defective and there was ptosis on the right side. The corneal reflexes were diminished and there was lower facial weakness on the right side. When he was sat up in bed he had great increase of hyperextension of the head, his eyes became more prominent, and his abdominal muscles contracted as though he were going to vomit, but he did not actually do so. His pulse at this time did not alter (rate 120). Movements of the left upper limb were weak and ataxic and there appeared to be relative astereognosis of the left hand. All the limbs were hypotonic, the left more than the right. All the tendon reflexes and the abdominal reflexes were absent, and the plantar reflexes were extensor. He was incontinent of urine and fæces and had frequent attacks of hiccough and of vomiting.

During the period of observation the boy gradually became dysarthric. Lumbar puncture had been done on June 26, 1930, because tuberculoma with tuberculous meningitis was suspected, and the 8 c.c. of fluid withdrawn contained 7 lymphocytes per cubic millimetre and 0·08 per cent. of protein. X-rays of the skull showed separation of the sutures and slight erosion of all the clinoid processes.

Diagnosis.—This case was considered to be most probably a medulloblastoma of the vermis, and it was regarded as particularly unfavourable because of the extent of involvement of the brain-stem, as indicated by the severe disturbance of lateral conjugate movement of the eyes and the obvious pyramidal signs. However, although the boy was practically blind, the condition of the fundi suggested that some sight might be regained if the lesion could be adequately dealt with, and operation was therefore decided upon, notwithstanding the child's poor condition and increasing drowsiness.

Operation, July 8, 1930: Intratracheal gas and oxygen. The cerebellum was exposed by the usual crossbow incision, after both lateral ventricles had been tapped and found to contain much fluid under greatly increased pressure (more than 650 mm. of cerebrospinal fluid). When the dura was opened the cisterna magna was seen to contain a soft red tongue of tumour which passed down through the foramen magnum to the lower border of the axis. It was necessary to remove the posterior arch of the atlas before this mass could be tilted out. The vermis was now divided in the middle line and the main part of the tumour was thus exposed. At its junction with the outgrowth into the cistern it was constricted by a vessel. The tumour was soft, and by means of suction about one-third of it was removed before the child's condition rendered it advisable to stop. After the usual closure a blood transfusion was given.

Post-operative course.—The child soon responded but was rather drowsy and he had frequent attacks of hiccoughs. Thirty hours after operation his temperature rose to 104·6°, breathing became jerky and irregular, and he died two hours later.

Summary of Necropsy. (*P.M.* 301, 1930.)

Metastatic glioma of leptomeninges of brain and spinal cord. Primary glioma (medulloblastoma) of vermis of cerebellum. Operation: subtentorial decompression and partial removal of tumour. Slight atheroma in mitral valve of heart. Mucous catarrh of stomach. Pink marrow in upper half of shaft and in neck of femur. Pallid, considerably wasted boy.

Macroscopic Examination.

Brain.—The brain was fixed fifteen hours after death. A partially excavated mass of soft pinkish white tumour (6 by 3 cm.) occupied the fourth ventricle and lower part of the vermis and extended into the dilated aqueduct of Sylvius (0·7 cm. in diameter). The tumour invaded the dorsal surface of the pons and medulla oblongata to a depth of 1·2 cm. From the left side of the medulla oblongata the tumour extended into the left cerebello-pontine angle. Here it formed a soft white mass (2·2 by 1·4 cm.) on the anterior surface of which ran the left lower cranial nerves. There was an isolated mass of tumour (1·0 by 0·6 cm.) in the highest point of the vermis. The surface of the cerebellum was completely covered by a semitranslucent white film of tumour tissue, which extended ventrally to cover the anterior surface of the pons. The film was thickest on the superior surface of the cerebellum, especially at its most anterior central part. On the inferior and anterior surfaces of the cerebellum there were also numerous, often confluent, opaque white plaques of tumour. Similar isolated plaques (up to 1·4 by 1·2 cm.) were seen on the surface of the right third frontal convolution, the right inferior temporal convolution and on the internal surface of each cerebral hemisphere.

The lateral ventricles were greatly dilated (capacity: right, 56 c.c.; left, 48 c.c.). The third ventricle was also dilated; its walls were everywhere smooth, except alongside the entrance of the aqueduct of Sylvius where there was a nodule of soft tumour tissue (0·2 cm. in diameter) continuous through the aqueduct with the main tumour. On the choroid plexus of the third ventricle were several soft white miliary deposits of tumour (0·2 by 0·1 cm.).

Spinal cord.—Below the eighth cervical segment the posterior surface of the cord was covered by a film of white granular tissue (up to 0·15 cm. thick) which frequently enveloped the posterior roots at their attachment to the cord. This film was attached to the cord but not to the overlying arachnoid, which itself showed numerous semitranslucent milky-white spots and confluent areas, especially in the region of the cauda equina.

Microscopic Examination.

The main tumour consists of a compact mass of cells (fig. 8) which have a small amount of very indefinite cytoplasm. The nuclei are rounded or oval and have a thick membrane and a fine chromatin net which is plentifully studded with nodes of varying size. The majority of nuclei contain from one to three small nucleoli. Multinucleate giant cells are present occasionally and mitotic figures are plentiful. With Mallory's phosphotungstic acid hæmatoxylin there is no evidence of neuroglia fibrils. The cells are refractory towards gold and do not show any further details of structure in silver preparations. In some areas the cells have each a fine short eosinophil process and tend to be arranged in the rosettes of Wright. In other places the cytoplasmic process is directed towards the wall of an adjacent blood-vessel. There is no reticulum apart from the walls of blood-vessels.

The tumour invades the adjacent cerebellum, the anterior corpora quadrigemina and the dorsal surface of the pons and medulla oblongata. The infiltration in the floor of the fourth ventricle extends downwards around the upper part of the central canal which, in the lower medulla oblongata, consists of a group of small canals lined with ependyma. The leptomeninges covering the mid-brain, the medulla and upper part of the vermis are densely infiltrated with growth and the invasion of the underlying tissue is both diffuse and perivascular in character. There is an increase of reticulum where the leptomeninges are infiltrated.

The cerebral metastases.—There are focal discrete areas of secondary growth in the leptomeninges of the cerebral hemispheres and over the floor of the third ventricle. In the larger of these the tumour cells spread downwards into the sulci, whence they invade the adjacent brain tissue both by direct extension and indirectly by infiltrating the perivascular sheaths of the perforating vessels. The cells lie both inside the sheaths and immediately outside in the brain substance. In a vessel near the floor of the third ventricle the cells are all outside the sheath. A small collection of tumour cells is situated at the base of the choroid plexus of the third ventricle, where it is suspended from the tela choroidea. The plexus itself, the adjacent fornix and the ependyma of the third ventricle are not affected.

The spinal metastases.—In a section through the twelfth thoracic segment there is diffuse infiltration of the subarachnoid space and of the subjacent pia over the dorsal and to a less extent over the lateral aspects of the cord. There also is a small collection of tumour cells at the opening of the ventral fissure. The superficial parts of the posterior columns are invaded from the pia, both by direct extension and by the growth of cells inwards around the perivascular spaces. The margin of the spinal cord is slightly crenated along the posterior border.

Comment.—The glioma described in this case is a medulloblastoma and exhibits the characteristic features of this type in its situation, its macroscopic and microscopic appearances and in the extensive distribution of metastatic deposits. The meningeal spread of this tumour affords an interesting comparison with Case 3, in which a massive intraventricular spread was demonstrated. In the case under discussion there was no ventricular spread anterior to the aqueduct of Sylvius, but the cells were distributed by the circulation of the fluid in the subarachnoid space. By this means they reached the base of the brain, the convexities of the cerebral hemispheres and the spinal cord. They also spread inwards by the velum interpositum to the attachment of the choroid plexus of the third ventricle.

The appearances at necropsy fully justified the misgivings that we had had about operating on this boy. The case was clearly a hopeless one, but in the present state of clinical knowledge it is not possible to refuse operation in a case of this type, especially when there is only slight rise of protein in the cerebrospinal fluid, lest in so doing a benign type of glioma that responds well to surgical treatment, as for example a cystic astrocytoma of the vermis, should be occasionally overlooked. The main hope of treatment in this type of case, and in cases like Case 2, would seem to be in massive radiation of the whole nervous system.

Case 5.—Glioma (differentiating medulloblastoma) of cerebellum. Ventricular and spinal metastases. Unusually long history of illness. Subtemporal decompression. Death.

History: Ronald J., aged 9 years, referred by Professor Ellis, was first seen on November 13, 1930. For six years he had had frequent attacks of morning vomiting associated with anorexia and listlessness. However, he was able to attend school regularly until one year before admission, when he began to suffer from daily attacks of frontal headache and unsteadiness in walking. The headaches became increasingly severe. Six months before admission he was sent home from school because he could not see the blackboard, and within a short time he was unable to see to read. He began to dream and to talk in his sleep. One month before admission he complained of pain in the left thigh, and he became very tired.

He had always been slightly undersized and plump. All his life he had suffered from frequency of micturition when cold, and his mother said that for some time he had passed an abnormally large amount of urine.

Examination: The patient was a somewhat drowsy boy of slightly short stature and normal intelligence (weight, 23·2 kilogrammes ; height, 1·22 metres). Pulse-rate, 66. His head was enlarged (circumference, 55·2 cm.), and there was tenderness in the suboccipital region, also pain on flexion of the neck. When standing, his head drooped towards the left shoulder. The left complexus muscle was rather prominent. Both optic discs showed papillœdema measuring 4 D., and on the right side there were streaks of bright yellowish white exudate converging from the edge of the disc towards the macula. Visual acuity: right, 0·5/18 ; left, 1/18. There was coarse nystagmus on lateral and upward movement of the eyes. Lateral conjugate movements of the eyes were considerably impaired, particularly to the left. He was very unsteady in walking and standing, tending to fall in any direction. There was no gross inco-ordination or weakness of his upper limbs. No tendon reflexes could be elicited. The abdominal reflexes were brisk and equal on the two sides, but the plantar reflexes were extensor. Postural sensibility was slightly impaired in the right big toe and there was relative astereognosis of the right hand. X-rays showed separation of the sutures and moderate enlargement of the sella turcica.

A diagnosis was made of tumour of the posterior fossa. The great disturbance of lateral conjugate movement of the eyes raised the question whether the tumour might not lie in front of rather than behind the floor of the fourth ventricle, but the long history was against this, and it was felt that we were most probably dealing with a slowly developing tumour of the vermis. On the eve of operation he had an attack of extensor rigidity of the limbs and hyperextension of the head, and from his nostrils there was a profuse discharge of watery fluid (? cerebro-spinal rhinorrhœa).

Operation, November 11, 1930: A cerebellar exploration was planned, but as a preliminary measure both lateral ventricles were tapped to determine whether there was symmetrical hydrocephalus. Owing, as was subsequently proved, to misdirection of the ventricular needle, the right ventricle could not be found, whereas the left ventricle contained abundant fluid under a pressure of 550 mm. of cerebro-spinal fluid. This observation raised the possibility that the tumour might be in the right hemisphere, and we therefore decided to temporize by doing a right subtemporal decompression. This was a bad error of judgment, for the clinical signs pointed to a lesion of the posterior fossa.

Two days later, a few hours before a cerebellar exploration was to have been done, the boy suddenly stopped breathing and died, in spite of immediate tapping of the left ventricle.

Summary of Necropsy. (*P.M.* 510, 1930.)

Metastatic glioma of ventricles and spinal subarachnoid space. Primary glioma of vermis of cerebellum. Operation: ventricular estimation and right subtemporal decompression. Very slight atheroma of mitral valve and aortic commissure. Considerable injection of trachea. Congestion, œdema, slight peribronchial hæmorrhages and acid digestion of posterior parts of lungs. Congestion of kidneys and liver. Numerous cysts (up to 2·3 cm. in diameter) in cortex and medulla of kidneys. Petechial hæmorrhage in first part of duodenum. Slight injection of ascending colon. Cheesy concretions in crypts of tonsils. Nodule of cartilage (0·4 cm. in diameter) in spongiosa of upper part of shaft of right femur. Well developed, well nourished boy. The spleen was not examined as it was used for injection experiments.

Macroscopic Examination.

Brain.—The brain was removed twenty-four hours after death. A tumour (6·6 by 6·2 by 3·8 cm.) occupied almost the whole of the vermis of the cerebellum (fig. 9) and presented on the posterior surface between the lateral lobes, and also immediately below the left choroid plexus of the fourth ventricle, where it formed a spherical nodule in contact with the left vagus and spinal accessory nerves and the adjacent left restiform body. The tumour was composed of soft, faintly granular, white tissue, in which were numerous small areas of hæmorrhage (0·1 cm. in diameter). In its centre there was a cavity (1 cm. in diameter) lined with blood-clot. The tumour was in most places sharply defined from the surrounding cerebellum, but it was attached to the lower part of the floor of the fourth ventricle. The upper part of the fourth ventricle was still patent and contained a nodular outgrowth from the main tumour which extended almost to the posterior end of the greatly dilated and shortened aqueduct of Sylvius (length 0·6 cm.; diameter 1·4 cm.). The pons and medulla oblongata were greatly flattened and displaced forwards, and each olive showed a groove where it was in contact with the corresponding vertebral artery.

There was severe internal hydrocephalus. The third and lateral ventricles were greatly dilated. The potential space of the fifth ventricle had been opened up by separation of the layers of the septum lucidum. This space connected with the lateral ventricles by rounded holes in each layer of the septum lucidum (fig. 9). All the convolutions were broad and the intervening sulci shallow. The tonsils of the cerebellum projected downwards a short distance through the foramen magnum, and there was great downward projection of each frontal lobe on to the cribriform plate of the ethmoid. No opening was found in the dura at this region.

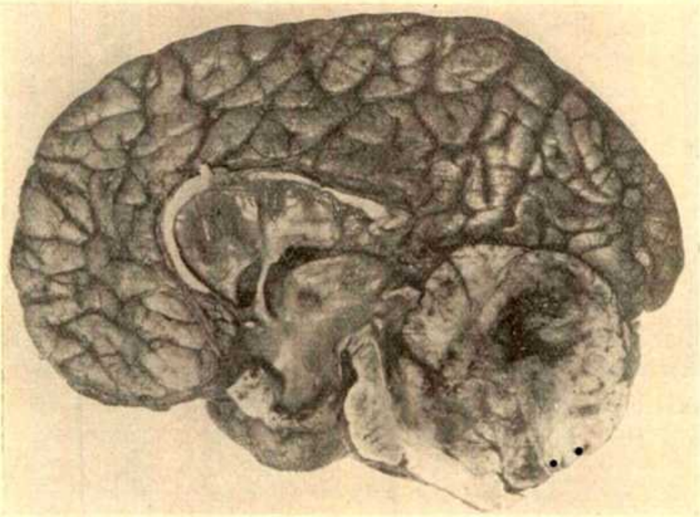

FIG. 9 (*Case* 5).—Right half of brain showing large primary glioma of cerebellum, and a metastatic nodule on the anterior wall of the dilated third ventricle. Immediately in front of the foramen of Monro the septum lucidum shows a large perforation.

Several other tumours, smaller than the primary tumour, were found in the ventricular system. On the anterior wall of the third ventricle there was a tumour (1·2 cm. in diameter) which filled the optic and infundibular recesses and surmounted the optic chiasm (fig. 9). On the floor of the anterior horn of the right lateral ventricle there was a plaque of tumour tissue (0·9 by 0·9 by 0·3 cm.). Two nodules were found on the walls of the left lateral ventricle, one (0·3 cm. in diameter) on the floor of the anterior horn, the other (0·5 cm. in diameter) on the posterior wall of the descending horn.

Spinal cord.—The arachnoid covering the posterior surface of the lower thoracic part of the spinal cord showed numerous opaque, greyish-white spots, about 0·1 cm. in diameter: On the anterior root of the fourth lumbar nerve on the right side, about 1 cm. below the level of the conus medullaris, there was a small grey nodule (0·25 cm. in diameter). The adjacent fifth lumbar anterior root was lightly adherent to this nodule.

Microscopic Examination.

The primary tumour.—The tumour is uniformly of a densely cellular character (fig. 10). These cells in general are small and possess scanty cytoplasm and oval or rounded nuclei. The nuclear membrane is stout and the chromatin net is of a close mesh and plentifully studded with deeply-stained nodes. There are from one to three nucleoli in most of the nuclei. The cytoplasm is eosinophil. It tends to be drawn out into short poorly-defined processes from one or both poles of the nucleus when the nucleus is elongated, and forms an indefinite fluffy zone when the nucleus is more spherical. A few multinucleate giant cells and occasional mitoses are present. There are no blepharoplasten. The architecture of the tumour varies with gradual transitions from one area to another. In some places the cells are closely clustered together with no architectural relationship to one another. In other places there is an evident formation into the rosettes of Wright. These are most conspicuously developed near the roof of the fourth ventricle. Frequently the rosettes are incomplete and the cells then appear in undulating palisades. More rarely the delicate non-fibrillated cytoplasmic processes of the cells radiate towards vessels, but without any attempt to form expansions where they terminate. In still other areas the cells are definitely of spindle form and lie together in bundles. In many of these cells there are fine sharply stained neuroglial fibrils in sections, stained by phosphotungstic acid hæmatoxylin (fig. 11). Apart from these intracellular fibrils there are in parts of the tumour other stouter neuroglial fibrils that run between the cells and appear to belong to certain large fibrillary astrocytes. These astrocytes are interpreted as belonging to the original cerebellar tissue that has suffered invasion by the tumour, since they are principally found near the edge of the tumour and there are no demonstrable transition forms between them and the tumour cells proper. They have an affinity for gold when treated by Cajal's method. The reticulum in the tumour is limited to the walls of the blood-vessels and the leptomeninges.

The invasive character of the tumour is demonstrated by a tongue-like process that extends into the fourth ventricle and is adherent in places to the floor of the ventricle. Beneath such areas the pons and medulla oblongata are also infiltrated with tumour cells. There is slight infiltration of the choroid plexus of the fourth ventricle at its point of attachment. The cerebellum is conspicuously infiltrated : the tumour reaches the leptomeninges at the posterior border of the vermis and extends to the depths of the sulci along the dorsal border in the mid-line,

The cerebral metastases.—The nodules in the third and lateral ventricles are all of similar appearance, and closely resemble the cerebellar tumour in their cytology. They occupy the subependymal tissue. The ependyma is reflected upwards at the borders of the nodules but is missing over their convexities. Near the larger nodules there are occasional microscopic deposits of tumour cells beneath the ependyma ; in such places the ependyma is not raised but shows a small break in continuity. This suggests that the tumour cells gain entry to the subependymal tissues through a rupture in the ependyma.

Such a process would doubtless be facilitated by internal hydrocephalus. The nodules are fairly discrete and the tumour cells do not invade the underlying tissues deeply. Thus, the cells forming the mass in the floor of the third ventricle do not extend to the leptomeninges at the base. A considerable number of giant cells and mitotic figures is present. There is less variety of cell type and arrangement than in the primary tumour; fibrillated spindle cells are absent and the tendency to form the rosettes of Wright is less marked on the whole. The majority of the cells are of the simplest form with a scanty cytoplasm that is drawn out into a short process at one point (pyriform cells). There is no reticulum save in the leptomeninges and in walls of blood-vessels.

The spinal metastases.—In the transverse section of the twelfth thoracic segment the subarachnoid space and the pia over the posterior columns are infiltrated somewhat scantily with tumour cells of round or pyriform type. The cells are slightly more abundant about the blood-vessels than elsewhere. There is no invasion of the substance of the cord by tumour.

The nodule on the anterior root of the fourth lumbar segment is composed of a discrete mass of round or pyriform tumour cells that surround the root and penetrate between the individual nerve-fibres, forming rows and small clusters. These cells are identical with the cells seen in the primary tumour and in the ventricular metastases.

Comment.—Most of the cells in the primary cerebellar tumour are medulloblasts, and the tumour must therefore be regarded as a medulloblastoma (fig. 10). The arrangement in rosettes of Wright in many places is characteristic of medulloblastoma, although not confined to this type of glioma. In some areas of the tumour spongioblasts with fibrillated processes (fig. 11) are so numerous as to indicate a degree of differentiation unusual in cerebellar medulloblastoma, though not unusual in medulloblastoma of the cerebrum (Cushing [7]). The metastases in this case emphasize the primitive character of the tumour, and have the cytological appearances of a typical medulloblastoma. The discrete character of the cerebral metastases is perhaps correlated with an unusually low grade of malignancy for this kind of glioma and provides a very striking contrast with the ventricular method of spread in Case 3.

The metastatic nodule in the floor of the third ventricle was possibly responsible for the persistent polyuria, in which case it can be inferred that metastasis occurred at a considerable interval of time before the death of the patient. The relatively slow growth of the tumour is doubtless to be correlated with the conspicuous tendency towards histological differentiation. Six years history of illness is most unusual in a case of cerebellar medulloblastoma.

GLIOBLASTOMA MULTIFORME.

Case 6. Glioma (glioblastoma multiforme) of left frontal lobe and corpus callosum. Death six weeks after onset of symptoms.

History: William A., an engine driver, aged 56, was admitted to the London Hospital under the care of Dr. Riddoch on August 14, 1930, in a semiconscious condition. He had always been healthy and, apart from depression following the death of his wife in October, 1929, had remained well until five weeks before admission, when he began to lose interest and to show signs of disorientation and impairment of comprehension. He continued at work for a further two weeks, but towards the end of that time was observed by his fireman to be in a dazed condition while driving his engine. Three weeks before admission he began to have severe headache in the occipital region extending down to the neck, and he complained of a noise in his head like the noise of an electric train. Micturition became difficult. He took to his bed, but the headaches grew worse for a week and he became more and more drowsy. His speech, which had hitherto been normal, became monosyllabic, slurred and wandering. For one week before admission he was unable to feed himself and was at times incontinent of urine.

Examination: On admission the patient was in a semicomatose condition. Temperature, 98·6° F. Pulse-rate, 110. Respirations were of Cheyne-Stokes character and his face and extremities were cyanosed. He was incontinent of urine and fæces. He resented passive movements of his head and his neck was rigid. There was slight bilateral papillœdema, more marked on the left side. The pupils were dilated and fixed. The right side of the face was paralysed and there was considerable weakness of the right upper and lower limbs. The abdominal reflexes were absent. Kernig's sign was present.

Lumbar puncture on the day of admission yielded 8 c.c. of slightly yellow fluid which formed a fine cobweb: 31 white cells per cubic millimetre (polymorphonuclear neutrophils 40 cent., lymphocytes 60 per cent.); protein, 0·5 per cent.; Wassermann reaction, negative.

The patient developed retention of urine and became progressively more deeply unconscious. He died on August 20, seven days after admission. The clinical diagnosis was that of leaking intracranial aneurysm.

Summary of Necropsy. (*P.M.* 361, 1930.)

Metastatic glioma of leptomeninges of spinal cord and cauda equina. Primary glioma of left frontal lobe and corpus callosum. Moderate hypertrophy of left ventricle of heart. Moderate atheroma of mitral valve, of commissure, descending thoracic and abdominal parts of aorta, and of coronary and common iliac arteries. Ante-mortem thrombus (11 by 1·5 cm.) in heart. Similar thrombus (17 cm. long) in left common and external iliac veins. Congestion of lungs. Thymus replaced by fat. Colloidal adenoma (1·5 cm. in diameter) in lower pole of right lobe of thyroid. Moderate congestion and parenchymatous degeneration of liver and kidneys. Slight œdema of spleen. Fatty infiltration of pancreas. Mucous catarrh and congestion of stomach. Obliteration by fibrosis of terminal part of vermiform appendix. Marginal and internal hæmorrhoids. Petechial hæmorrhages in mucosa of urinary bladder. Black gravel in prostate. Congestion of fatty marrow of upper half of shaft of left femur. Papilloma of skin above inner canthus of right eye. Valvular patent foramen ovale (*ca.* 0·5 cm. in. diameter). Well nourished, well developed man, showing frontal and vertical alopecia.

Macroscopic Examination.

Brain.—There was venous engorgement of the surface of the cerebral hemispheres. A tumour (5·5 by 4 by 4·7 cm. from before backwards) occupied the head of the left caudate nucleus, the adjacent part of the genu and anterior third of the body of the corpus callosum, and the adjacent white matter of the left frontal lobe. It consisted for the most part of soft greyish-white granular tissue, but was in places opaque yellow. The frontal horn of the left ventricle was situated immediately behind and below the tumour, and was compressed so as to form a crescentic slit. In this region its ependymal lining, in an area 1·5 cm. diameter, presented several glistening granulations. The body of the left lateral ventricle was obliterated by downward projection of the tumour in the body of the corpus callosum. This part of the tumour had displaced the septum lucidum and fornix to the right, and was adherent to the fornix in places. The posterior horn of the right lateral ventricle was slightly dilated but there was no other evidence of hydrocephalus. The third and fourth ventricles appeared normal.

On the ventral aspect of the left lateral lobe of the cerebellum the leptomeninges were opaque and slightly raised over small ill-defined confluent areas which together measured 1·8 by 1·2 cm. On the dorsal aspect the leptomeninges over the vermis contained a few ill-defined greyish-yellow nodules (up to 0·2 cm. in diameter).

Spinal cord.—The leptomeninges of the spinal cord were extensively infiltrated by opaque gelatinous grey growth. This growth formed rounded nodules on the posterior roots at various levels, and in places it formed a coat of confluent nodules over the posterior surface of the cord and adjacent nerve roots. The cervical part of the cord showed very little deposit, but there were a few small nodules (up to 0·5 cm. in diameter) over the origins and along the course of some posterior roots, especially on the second cervical root on the left side. From the eighth cervical to ninth thoracic segments the cord was covered by a continuous sheet of tumour tissue, and below that its surface was studded by grey bosses of growth (up to 1·0 by 0·7 cm.). On the cauda equina the deposit was not quite so heavy; numerous nodules of soft grey growth (up to 1·0 by 0·5 cm.) were attached to the roots, and there was also a diffuse deposit in the arachnoidea, which was most conspicuous at the points of exit of the posterior nerve-roots through the dura. The anterior surface of the cord showed a few diffuse areas of infiltration (up to 1·2 by 0·3 cm.), mostly situated in the middle line over the linea splendens in the lumbar region.

Microscopic Examination.

The primary tumour.—The greater part of the centre of the tumour in the left frontal lobe and genu of the corpus callosum is necrotic. Outside this the tumour, in the frontal lobe, is of loose texture and is composed of cells with round, oval or spindle-shaped nuclei. the majority of which have thin membranes, a fine chromatin net beset with a few nodes of variable size, and one or two nucleoli. Some of the nuclei, however, contain much more chromatin. The cells are stellate or spindle and their cytoplasmic processes frequently contain neuroglial fibrils when stained by Mallory's method. There is a moderate number of multinucleate giant cells but mitotic figures are not present. In some cells there are one or two dots in the cytoplasm, near the nucleus, which resemble blepharoplasten but are probably diplosomes because in the giant cells there are sometimes as many as five or six. Palisades of spindle cells are sometimes present at the border of an area of necrosis, but there is no special arrangement of the cells in relation to vessels. In the corpus callosum the cells are closely packed; they are of spindle form and contain conspicuous neuroglial fibrils (fig. 12). These cells are impregnated by Cajal's method. In the more spongy parts of the tumour there are many typical fibrillary astrocytes.

The margin of the necrotic tissue is in places honeycombed with a number of small, greatly engorged, thin-walled vessels, in some of which there is endothelial proliferation. In this region also there is considerable fatty degeneration. Where the tumour projects into the left ventricle the ependyma has been replaced by growth. There are miliary implantations of tumour tissue in the ependyma adjacent to the primary mass.

Cerebellar metastases.—The leptomeninges over the cerebellum are in places infiltrated with finely fibrillated glial cells of stellate and spindle form, similar to those observed in the primary tumour. These cells tend to be arranged with their long axes at right angles to blood-vessels and to the surface of the arachnoid membrane. There is a conspicuous endothelial proliferation in the small blood-vessels that lie in this tissue. The amount of reticulum is scanty. The tumour cells do not invade the cerebellum nor penetrate into the sulci.

A small nodule in the leptomeninges over the vermis proves to be a minute psammomatous endothelioma arising in the arachnoid.

The spinal metastases.—In the second thoracic segment the subarachnoid space is occupied by gliomatous tissue similar to that seen in the leptomeninges of the cerebellum. The tissue is relatively thin over the ventral surface of the cord but increases over the lateral aspects, and over the posterior columns it reaches a maximum depth equivalent to a quarter of the total depth of the posterior columns. There is no invasion of the cord. In the twelfth thoracic segment a boss of similar tissue is seen surrounding the right dorsal root (fig. 13). The tissue is loose in texture and contains many stellate cells and bands of spindle cells that are arranged at right angles to the arachnoid membrane. Amongst these are occasional multinucleate forms. The tissue is moderately vascular and there is a conspicuous degree of endothelial proliferation in the vessel walls.

In the cauda equina the deposits present a similar appearance. In these there is no evidence of fatty degeneration. The cells are not impregnated by Cajal's method, but with Hortega's silver carbonate method for astrocytes a great number of fibrillary astrocytes is seen (fig. 14). Many of these have foot-plates in relation to strands of collagen and adjacent nerve bundles. Amongst the astrocytes are many spindle bipolar forms.

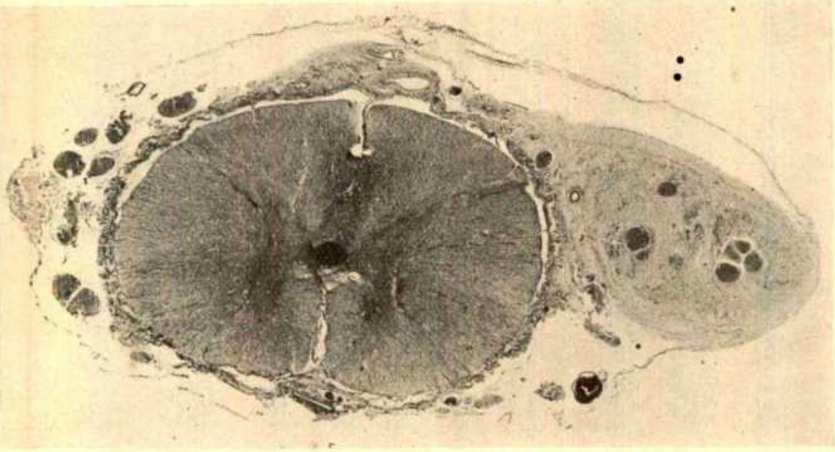

FIG. 13 (*Case* 6).—Transverse section of twelfth thoracic segment. Metastatic mass of growth in subarachnoid space on the right. Phosphotungstic acid hæmatoxylin. × 8.

Comment.—In judging the nature of this glioma the form of the tumour cells in the spinal deposits is important. In these deposits many of the astrocytes are attached by foot-plates to the collagen strands and nerve fibres. This proves that they are cells which have grown *in situ* and have not merely been carried to their present position. From the macroscopic and microscopic appearances it is impossible to regard the deposits as developmental rests, and developmental rests have never been recorded over the cauda equina as far as we are aware. There can be no doubt that the deposits are metastases.

In the primary tumour the polymorphism of cell forms, the presence of giant cells and the extensive necrosis are in accordance with the descriptions given by Bailey and others of glioblastoma multiforme. The tumour has, therefore, been provisionally labelled as an example of this type. The very large proportion of astrocytes, both in the primary tumour and in the metastases, raises the question as to whether the tumour should not be regarded as an astrocytoma that has undergone anaplasia with the development of more embryonic glial forms and a higher order of malignancy. Such a change occurring in an astrocytoma has already been reported by Bailey and Cushing [4]. The predominance of elongated spindle forms in the corpus callosum (fig. 12) is perhaps the result of pressure upon the tumour in this site forcing the cells into a minimal space. A parallel observation is afforded by Case 7 in which a large proportion of spindle cells was present in an astrocytoma situated in the left optic thalamus. The variations in morphology of gliomas that may be produced by the varying texture of different parts of the brain is a subject worthy of closer study.

In the metastases the tumour cells occupy the subarachnoid space. Here they have room to grow, and it is probable that they show more clearly their true form than when multiplying in the substance of the brain. Their astrocytic character is very conspicuous (fig. 14). Had the growth in the brain alone been available it might have been argued that the astrocytes were formed by a reaction of normal tissue when invaded by tumour cells. The structure of the spinal metastases effectively rules out this objection.

ASTROCYTOMA.

Case 7.—This case has been previously reported by us [16], and it is only necessary, therefore, to mention the main facts here. The case was one of astrocytoma in the right optic thalamus in a man aged 28. The tumour invaded the lumen of the third ventricle and extended up to the leptomeninges between the corpus callosum and pineal gland. The inner surface of the spinal arachnoidea was studded with numerous glistening grey nodules, up to 0·1 cm. in diameter, which on section proved to possess the same structure as the primary tumour. Doubt has been cast upon our interpretation of these nodules by Bailey and Bucy [3], who consider that "it is a little difficult to believe that an astrocytoma could produce such an infiltration or metastasis." They prefer to believe that the nodules we described were islands of neuroglia analogous to those found in the spinal arachnoidea by Wolbach [21] and others in cases in which there was no primary glioma of the brain, and thus no question of metastases in the spinal cord or its membranes. This interpretation of our case is incorrect, for, as the original case report stated, numerous nodules of tissue identical with those in the spinal arachnoidea were found in the arachnoidea over the pineal body, near the primary tumour. These nodules were identical in structure with the parent tumour, and they were only found in the cerebral subarachnoid space in the vicinity of the primary tumour. Moreover, in the cases alluded to by Bailey and Bucy the neuroglial nests were associated with other gross developmental abnormalities of the central nervous system, such as tuberose sclerosis and, as far as we are aware, they have not been found in an otherwise normal central nervous system.

EPENDYMAL GLIOMA.

Case 8.—Ependymal glioma of cerebellar vermis extending through the foramen magnum. Progressive quadriplegia. Death.

History: Alfred D., aged 59, a retired police officer, was admitted to the Hospital for Epilepsy and Paralysis, Maida Vale, under the care of Dr. Russell Brain, on November 8, 1929. He had contracted syphilis at the age of 26, but apart from this had been quite well until May, 1926, when he began to have numbness in the tips of the fingers and weakness of the right hand. The numbness gradually extended up to the right elbow, and two or three months later the right side of the neck was similarly affected. In May, 1927, he began to drag his left foot occasionally. He noticed that his "stomach muscles" seemed stiff and he complained of a lifeless kind of feeling. There does not appear to have been much further change until July, 1929, when his walking became difficult owing to loss of power, and micturition became frequent. His left upper limb was also affected at this time.

Examination: The following neurological signs were found: Slight relative analgesia on the left side of the face. Weakness and wasting of all the muscles of both upper limbs and shoulder-girdles, more marked on the left side. Weakness of the abdominal muscles. Weakness and slight spasticity of both lower limbs. Exaggeration of all tendon-jerks except the right ankle-jerk, which was absent. Absence of abdominal reflexes. Bilateral ankle clonus and extensor plantar reflexes. Sensibility to light touch was preserved. There was patchy analgesia to pin-prick over the radial borders of both upper limbs, and in the lower limbs. Sensibility to heat and cold was lost up to the fifth cervical segmental level on both sides. Postural sense was lost in the digits and appreciation of vibration was diminished in both lower limbs, especially on the left side. The Wassermann reaction in the blood was negative.

Lumbar puncture yielded fluid clear and colourless. Total protein, 0·04 per cent. approximately; 1 to 2 cells per cubic millimetre. Wassermann reaction negative.

A diagnosis of syringomyelia was made. By November 24 he was definitely weaker and there was occasional incontinence of urine. On December 23, increasing helplessness was recorded. There appeared to be definite reduction in discrimination between sharp and blunt, especially in the lower limbs. At times there was cutaneous tenderness in the left lower limb and left side of the trunk. On January 14, 1930, his general condition was much worse. There was marked respiratory distress, cyanosis and laryngeal rattle. He died on this day.

Macroscopic Examination.

Post-mortem examination was limited to the brain and spinal cord.

Brain.—A solid, firm tongue-shaped tumour (5 cm. long by 3·5 cm. wide by 2 cm. deep) projected from beneath the lower extremity of the vermis to fill the cisterna magna and extend over the posterior surface of the medulla oblongata and first segment of the cervical cord. The surface of the upper part of the tumour was broken up into cauliflower-like nodules, but the lower portion had a smooth greyish-yellow glistening surface marked by a few fine blood-vessels. On median sagittal section the tumour appeared as a triangular mass, the base of which rested against the posterior surface of the flattened medulla and upper cervical cord. It extended into the lower part of the fourth ventricle, reaching as high as the lower borders of the choroid plexuses to which it was adherent. The margins of the growth were everywhere sharply defined. The cut surface was flat, firm and glistening greyish-white and was broken up into lobules (up to 0·2 cm. diameter) by a fine grey network. It was gritty to the knife in many places, especially near its posterior surface. The remainder of the brain appeared normal.

Spinal cord.—Beneath the arachnoid membrane on the posterior surface of the fifth thoracic segment there was an inconspicuous group of glistening pinhead nodules which were only observed on close examination after fixation. In the light of previous experience these were suspected of being fragments of metastatic tissue.

Microscopic Examination.

The median cut surface of the tumour was examined in three blocks and transverse sections were taken from the lower part of the medulla oblongata and from the fifth thoracic segment of the cord.

The primary tumour.—The tumour is composed of a solid mass of cells which vary somewhat in appearance and arrangement in different places. By far the greatest part is made up of long spindle-shaped cells (fig. 15), which tend to lie in interlacing bundles and often arrange themselves at right angles to blood-vessels and strands of collagen. Their cytoplasm is full of stout neuroglial fibrils (phosphotungstic acid hæmatoxylin). There is a variable number of such fibrils in each cell; in some there are as many as twelve. These fibrils are readily demonstrated with silver, but are only faintly stained by Cajal's gold chloride sublimate. In addition, there are in the majority of the cells conspicuous blepharoplasten situated in the cytoplasm close to the nucleus. The nuclei are round or oval and have a delicate membrane and chromatin net beset with a moderate number of nodes. From one to three nucleoli are present in the majority of cells. There is no evidence of foot-plates in connection with these cells in either Cajal or silver preparations. In other parts of the tumour there are small, poorly-defined areas composed of irregular groups of polygonal cells with round nuclei (fig. 16). These cells have no processes and no neuroglial fibrils. Occasionally they appear to be grouped about a small lumen. In such places the blepharoplasten are collected in the cytoplasm adjacent to this lumen, but cilia are not demonstrable. There is considerable "calcification" of the tumour, especially at the periphery and adjacent to the posterior border. The blood-vessels, which are not numerous, frequently show a proliferation of endothelial cells, and many have undergone a hyaline collagenous thickening. The blood-vessels and a scanty stroma of collagen and reticulum divide the tumour into poorly-defined lobules. Apart from this stroma there is no reticulum in the tumour.

The tumour tissue involves the ependyma of the roof of the fourth ventricle, but does not invade the choroid plexuses, which appear normal. The posterior border of the tumour extends into the leptomeninges as small polypoid projections. The tissue forming these projections and the adjacent tumour is extremely rich in neuroglial fibrils.

The spinal metastases.—In the section of the fifth thoracic segment there are two small oval nodules of solid tumour tissue situated immediately beneath but not attached to the arachnoid membrane over the posterior aspect of the cord. These nodules are chiefly composed of interwoven neuroglial fibrils, amongst which are a few nuclei similar to those of the primary tumour. Each nucleus is surrounded by a little ill-defined cytoplasm. In one of the cells a group of three blepharoplasten lying in a clear halo is seen near the nucleus. Neither collagen fibres nor vessels are seen in these nodules.

Comment.—This tumour is an ependymal glioma and is particularly interesting because its cells contain conspicuous fibrillæ (fig 15). It is generally supposed that the presence of such fibrillæ in neuroglia indicates that the cells are astrocytes, but our experience has shown that ependymal spongioblasts are more commonly and more conspicuously fibrillated than has hitherto been recognized. In this tumour, for example, the cells are clearly not astrocytic in nature, for they do not form foot-plates and they are not impregnated by Cajal's method. Further, they contain conspicuous blepharoplasten, and in some parts of the tumour tend to arrange themselves in the rosettes of Bailey. The site and macroscopic appearances are fully in accord with the histological diagnosis of ependymoma.

The nodules in the subarachnoid space of the spinal cord presented meagre material for microscopic diagnosis. They bore a considerable resemblance, however, to the parent tumour, and the finding of blepharoplasten established their origin. The fact that metastasis could occur in so relatively benign a tumour lends strong support to our view that the potentiality of a glioma to disseminate metastases in the cerebrospinal pathway depends as much upon the site of the tumour in relation to this pathway as upon the intrinsic malignancy of its component cells.

Although ependymal gliomas are of slow growth and relatively benign, it is not unlikely that they frequently give rise to spinal metastases, for when they arise in relation to the fourth ventricle, a common site, they tend to project into the cisterna magna and even into the subarachnoid space of the cord, from which position spinal metastases can easily occur. Spiller [18] recorded a case of ependymoma of the posterior part of the fourth ventricle which spread down on the cord to the sixth cervical segment; another but smaller tumour of similar structure was found on the lower thoracic region of the cord "and was probably a metastatic growth." Bailey [1] stated that he had examined sections of this tumour and was convinced that it arose from ependymal cells in the floor of the fourth ventricle.

DISCUSSION.

Our search for spinal metastases began only in 1928, and since then we have found them in eight out of twenty-two cases of cerebral glioma in which both brain and cord were examined. In addition, we have found during the same period one case of sarcomatosis (or possibly gliomatosis) of the leptomeninges of both brain and cord without a demonstrable primary tumour, one case of bilateral acoustic nerve tumours, in which there were numerous unsuspected spinal ependymomas and tumours of the meninges and spinal nerve roots, and one case of pituitary adenoma with dissemination of free tumour cells in the spinal subarachnoid space. From our cases it appears that spinal or cerebral metastases may be found in the following varieties of glioma: medulloblastoma, neuro-epithelioma of the retina, glioblastoma multiforme, astrocytoma and ependymoma.

Other varieties can be added from cases reported in the literature. Thus, van Wagenen [20] has made it clear that *papillomas of the choroid plexus* may also be disseminated in the way we have described. In one of his cases the primary tumour filled the greater part of the left lateral and third ventricles. There were "many small implants" in the left temporal horn and a solitary nodule of similar tumour tissue in the occipital pole of the right lateral ventricle. The macroscopic and microscopic appearances of this type of tumour are so characteristic that van Wagenen is able to cite from the literature other cases in which a primary papilloma of one or other choroid plexus gave rise to similar ventricular or subarachnoid implants. In one of these, reported by Töppich [19], a papilloma occupying the fourth ventricle was associated with numerous secondary deposits in the cerebral and cerebellar leptomeninges and, in addition, the subarachnoid space from the middle thoracic region to the cauda equina contained very numerous, often confluent masses of tumour. Davis and Cushing [8] believe that the choroid plexus tumours are usually single and that they may be confused with papillary ependymoma, a tumour that "tends to seed itself." We have, however, in this Institute an undoubted papilloma of the fourth ventricle (P.M. 224, 1923), and in this specimen the roof of the fourth ventricle is studded with minute nodules of growth. The spinal cord was not examined. There can be no question but that this type of tumour is liable to give rise to metastases.

Oligodendroglioma may also in certain circumstances give rise to metastases. Thus in a case previously reported [6] from Dr. Cushing's clinic, a man aged 23 died suddenly three and a half years after removal of an oligodendroglioma of the right frontal lobe, and at necropsy was found to have secondary tumours in the occipital horns of both lateral ventricles and in the fourth ventricle.[1] [2]

Earlier literature contains many reports of cases in which gliomas gave rise to metastases, but most of the histological descriptions are inadequate for the purposes of modern classification.

The extent of metastasis varies greatly in different varieties of glioma and is approximately proportional to the malignancy of the primary tumour, estimated by clinical and histological criteria. Thus in medulloblastoma and neuro-epithelioma of the retina the metastases are profuse. These tumours, indeed, appear to spread as much by direct extension as by metastasis. Thus in Case 3 (medulloblastoma) tumour tissue was found as a continuous sheet over the whole surface of the third and lateral ventricles, and there were isolated nodules of tumour in the spinal subarachnoid space. In Case 2 (neuro-epithelioma of the retina) there was a continuous sheet of tumour tissue throughout the basal cisterns and subarachnoid space of the cord, while isolated nodules of tumour were found on the convex surface of the brain and in the ventricles. The metastases of these tumours alone (Cases 2, 3 and 4) infiltrate the nerve tissue of brain and cord from their position in the meninges, though in other less malignant types the metastases infiltrate the meninges, the walls of the ventricles and, in Case 5, the sheaths of spinal nerve roots.

In glioblastoma multiforme (Case 6), and in another tumour of primitive type as yet unclassified (Case 1), the metastases were large and surrounded the cord. In Case 5, a medulloblastoma of less malignant type than in Cases 3 and 4, there were large isolated nodules of tumour in the third and lateral ventricles, and there were smaller isolated flecks of metastatic tissue in the spinal subarachnoid space. In the two other cases (Case 7, astrocytoma, and Case 8, ependymoma) the metastases were scarcely visible to the naked eye and appeared under the microscope as small nodules lightly attached to the arachnoid and evidently possessing no powers of invasion. Criticism has been levelled by Bailey and Bucy against our diagnosis of the spinal nodules as metastases in Case 7. This is answered in the comment on the case as reported in this paper. The spinal nodules found in the case of ependymoma (Case 8) consisted for the most part of neuroglial fibrils, but blepharoplasten were found, thereby establishing their relationship to the primary tumour.

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[1] This case has also been reported by Bailey and Bucy [2] in their study of oligodendrogliomas.

[2] Recently Purdon Martin (*Brain*, 1931, **54**, 334) has reported another case of oligodendroglioma that spread, partly in continuity and partly by metastasis, through the greater part of the ventricular system.

THE SPREAD OF GLIOMAS.

Gliomas may spread in continuity or by metastasis. We are not directly concerned in this paper with spread in continuity, but it is necessary to mention briefly some of the features of that process, inasmuch as the tumours that we are considering often spread in the subarachnoid space in this way. When enclosed by nerve tissues most gliomas appear to spread centrifugally by direct extension independently of vascular channels. But when a tumour, especially one of the more malignant varieties of glioma, reaches the leptomeninges, it may again invade the brain from the surface, not only by direct extension but also by spreading along the perivascular spaces. In this position also a glioma may extend through the leptomeninges and in rare instances may even invade the adjacent dura and bone. We have studied one example of glioblastoma multiforme situated in the temporal lobe which invaded the tegmen tympani.

Metastases from gliomas appear to be limited to the central nervous system and to be disseminated by the cerebrospinal fluid. They occur in the walls of the ventricles or in the pia arachnoid of the brain and cord. In the ventricles the metastases vary in size from nodules that are easily seen with the naked eye to microscopic collections of cells. The ependyma is raised up at the margins of the nodules, but is usually deficient over their summits. The metastases undoubtedly reach this site by way of the ventricular cavities; they do not appear to be related to the subependymal vessels. All the evidence suggests that implants from the primary tumour may gain entrance to the subependymal glia by splits or cracks in the ependyma such as are frequently seen in severe hydrocephalus. It is also conceivable that they may be deposited upon and replace the intact ependyma, but histological evidence of such a process has not been seen. Internal hydrocephalus was demonstrated at some period in all of our cases in which ventricular spread occurred.

Spinal metastases appear to arise by implantation along the subarachnoid space, for they are limited to, or at least are most numerous in, that situation. They are also more frequently seen on the dorsal than on the ventral surface of the cord, from which it may be surmised that gravity plays a considerable part in their distribution. Gravity may also account for the situation in the occipital and temporal horns of the ventricular metastases found both in Case 5 and in the example of oligodendroglioma of the right frontal lobe cited above.

A perusal of our cases shows that, with the exception of Case 2, all the primary tumours had reached the surface of the ventricular system although they varied considerably in malignancy. Case 2 was a glioma of the retina which spread rapidly along the optic nerve to reach the cisterna chiasmaticus. There can be no doubt that access to the ventricular system or basal cisterns is a circumstance of primary importance in the production of metastases. The intrinsic malignancy of the tumour plays its part in promoting rapid growth to the ventricular or subarachnoid surface of the brain and thereafter in the formation of potential metastatic tissue, but a relatively benign tumour that arises in or near these surfaces will also be liable to seed itself in proportion to its accessibility and the exuberance of its growth. The only spread of relatively benign primary tumours of other parts of the body that is at all comparable to this appears to be that of papilloma of the bladder, or that of pseudomucinous cystadenoma of the ovary in the peritoneal cavity.

HISTOLOGICAL FEATURES OF METASTASES.

There is a certain amount of evidence suggesting that gliomas vary in their morphology to some extent in accordance with the texture of the nervous tissue in which they grow. Thus, glial tumour cells invading the white matter of the brain tend to adopt a spindle form and to lie in parallel bundles between the myelin sheaths. They also tend to assume a spindle form in areas where the brain is at all extensively replaced by connective tissue. Allowances have to be made for such circumstances in determining the nature of the type cell in gliomas. Considerable light may be shed on this problem in individual cases by a study of the cytological features of the metastases, because it is then possible to see the tumour cells growing on a free surface and untrammelled by their supporting tissue. In the more malignant tumours (Cases 2, 3, 4, 5) the metastases closely resembled the parent tumour. In Case 1 study of the cells in the leptomeninges was of great assistance in determining the morphology of the tumour cells, inasmuch as they were better preserved and the character of their processes was more easily seen (fig. 2).

In Case 6, glioblastoma multiforme, the metastases were of the greatest value. The primary tumour in the corpus callosum was composed of fibrillated cells, the majority of which were of spindle form (fig. 12) while others were astrocytes. It was difficult to determine how many of the astrocytes observed were true tumour cells and how many were the result of glial reaction in the invaded brain tissue. The structure of the metastases, however, clearly showed that the majority of the tumour cells were adult fibrillary astrocytes (fig. 14). Many of these had developed *in situ* because their foot-plates were attached to the collagen sheaths of the nerve roots and other fixed structures in their environment.

In the less rapidly-growing kinds of tumour, the presence of gliomatous metastases in the leptomeninges leads to a focal proliferation of the connective tissue with increase of reticulum fibres. In some places these fibres ramify between the individual tumour cells, but in others cellular areas devoid of reticulum are found. The appearances produced by this proliferative reaction of connective tissue resemble at times those seen in so-called "primary sarcomatosis" of the meninges. In this condition there is a profuse production of reticulum and the tumour cells tend to invade the underlying brain by the perivascular sheaths alone. These features have been regarded as characteristic of sarcomatosis, but our cases of gliomatosis show that they are not so.

Associated with gliomatosis there is often a proliferation of the meningeal capillaries furnishing the neoplastic tissue with an increased blood-supply. This was conspicuous in Case 6. The capillaries in this example often showed also an endothelial proliferation as in the primary tumour.

Metastatic deposits often undergo focal degeneration and necrosis. This is accompanied by an infiltration in and about such areas with neutrophil leucocytes. More rarely (Case 1) plasma cells are also present.

No reaction on the part of the ependyma or of the subependymal glia has been observed in connection with ventricular metastases.

Clinical Significance.

Lumbar puncture was done at some stage of the illness in five of the eight cases described above and the total protein content was found to be raised in three cases, particularly in Cases 1 (unclassified glioma) and 6 (glioblastoma multiforme), where it reached 0·5 per cent. In both of these cases there were extensive spinal metastases, but in Case 6 the primary glioblastoma multiforme of the corpus callosum had spread to the surface of the left lateral ventricle, and the rise of protein in the cerebro-spinal fluid may have been in part due to bleeding from the primary tumour into the ventricle. We have observed a case of vascular glioblastoma multiforme of the corpus callosum in which the protein content of the spinal fluid was 0·15 per cent., though no spinal metastases were found at necropsy. A similar rise of protein in the cerebro-spinal fluid obtained by lumbar puncture has been observed by us in association with tumours of the cerebello-pontine angle, in one case of dural endothelioma of the sphenoidal ridge (0·25 per cent.), and in a glioma (spongioblastoma unipolare) invading the left lateral ventricle. It is thus clear that increase of protein in the spinal fluid in cases of intracranial tumour does not necessarily indicate the presence of spinal metastases. However, it should probably be regarded as suggestive of that complication when it is encountered in children, for the other causes of such an increase occur almost exclusively in adults. Our cases also show clearly that increase of protein in the spinal fluid, in the presence of signs and symptoms suggesting spinal metastases, does not indicate that the primary tumour is always a medulloblastoma of the cerebellum.

Tumour cells were not recognized in the spinal fluid in any of our cases, though recent observation of tumour cells in the spinal fluid from a case of rapidly-growing pituitary adenoma suggests that they might be found more often if looked for carefully. The presence in the spinal fluid of mononuclear cells other than lymphocytes should always arouse suspicion of tumour.

The metastasis in the third ventricle in Case 8 probably accounted for the polyuria observed before operation, but apart from that no symptoms were observed in our cases that could be definitely attributed to the cerebral metastases. Bielschowsky and Unger [5] reported a case in which a tumour was removed from the left motor area, and subsequent necropsy showed that the tumour removed at operation was a metastasis from a primary papilloma of the choroid plexus of the fourth ventricle

It is remarkable that in our cases spinal metastases gave rise to few or no signs, even when the cord was almost entirely surrounded by large masses of tumour. Cushing [7] has reported several cases in which signs of compression were produced by spinal metastases of cerebellar medulloblastoma after removal of the primary tumour. In one of his cases Elsberg [9] removed a metastatic tumour from the cauda equina fourteen months after Cushing had removed the primary tumour. The patient died six months later from recurrence in the cerebellum.[1] So far as we are aware clinical symptoms from spinal metastases have hitherto been observed only in the malignant varieties of glioma, but with the increasing success of attempts to remove completely the more benign gliomas it is possible that spinal metastases from these tumours may have time to grow to such a size as to produce symptoms. There are, of course, other diffuse tumours of the leptomeninges that may give rise to spinal symptoms, for example, primary sarcomatosis, or secondary carcinomatosis of the leptomeninges. Some writers (Ford and Firor [12]) have sought to describe distinctive symptom complexes for primary sarcomatosis of the leptomeninges, but it is clear from their own work that the clinical features only serve to indicate the presence of diffuse tumours of the leptomeninges and do not necessarily indicate the pathological type of tumour.

The proposition has to be considered that metastasis may be promoted in certain cases by operative interference. This probability arises chiefly in conjunction with tumours in the neighbourhood of the fourth ventricle. Thus, in a case recorded in this Institute a patient died a few hours after removal from the posterior fossa of a meningeal tumour which had become somewhat adherent to the adjacent cerebellum. There was considerable gliosis of the cerebellar margin. On examination of the spinal cord, four minute pin-point and pin-head nodules were observed under the arachnoid membrane over the dorsal surface of the sixth thoracic segment. On microscopic examination these proved to be free-lying nodules of neuroglia identical in appearance with the cerebellar tissue that had been adherent to the meningeal tumour. After removal of gliomas that are in contact with the basal cisterns, especially the cisterna magna or the walls of the ventricles, the question of prophylactic irradiation of the spinal canal and ventricular regions should receive consideration.

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[1] Collier (*Brain*, 1904, **27**, 506) reported a case in which spinal metastases arose from a tumour in the neighbourhood of the fourth ventricle. Severe shooting pains occurred in all the limbs and later the knee, wrist and elbow jerks were lost, and the fifth and sixth cervical nerves were completely paralysed.

Study of cases such as we have described in this paper will help considerably in enabling clinicians to distinguish between the cases that can be benefited by surgical treatment and those that are hopeless. Operation is not necessarily contra-indicated when metastases are found, for it still remains to be seen whether the small metastases observed in the more benign gliomas will grow so as to produce symptoms. But in the presence of extensive metastases malignant gliomas, like those described in Case 4, are clearly not suitable tumours for operative treatment. To consolidate the great advances recently made in neuro-surgery, it is necessary that we should learn to recognize such cases without recourse to operation.

SUMMARY.

Eight cases are reported in which a primary glioma of the brain was associated with subarachnoid spinal metastases and, with the exception of Cases 7 and 8, with intracranial metastases as well. These cases include the less malignant and more highly differentiated types of glioma, such as astrocytoma and ependymoma, as well as the more primitive and malignant types, such as neuro-epithelioma of the retina, medulloblastoma and glioblastoma multiforme.

It is shown that the proximity of a glioma either to the ventricular system or to the basal cisterns is probably as important in promoting metastases as the intrinsic malignancy of the tumour cells.

The secondary deposits in the subarachnoid space have room to grow freely, and a study of their cytology sometimes throws considerable light on the nature of the primary growth.

Attention is drawn to the alterations in the cerebrospinal fluid and other clinical disturbances that may arise in these cases.

Inasmuch as spinal metastases have been observed in eight out of twenty-two consecutive full necropsies in cases of glioma, it is evident that the frequency of this process has hitherto been underestimated.

We desire to thank Professor H. M. Turnbull for his help in the preparation of this paper and our colleagues for permission to use the clinical records of their cases.

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A CASE OF CONGENITAL ELEVATION OF THE SCAPULA (SPRENGEL'S DEFORMITY) WITH DEFECT OF THE CERVICAL SPINE ASSOCIATED WITH SYRINGOMYELIA.

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CASES of Sprengel's deformity of the shoulder, a comparatively rare condition, have been reported associated with a great variety of developmental abnormalities. As far as could be ascertained, however, only one case has been recorded in which the deformity was associated with sensory disturbance and paraplegia [1].

A male, aged 34, an electrician, was admitted under Dr. Gordon Holmes, to the National Hospital, Queen Square. He complained of numbness and weakness of the hands, and numbness, weakness and stiffness of the legs. The disability commenced about two years previously. He stated he was born with wry-neck and wore an iron frame up to the age of 12. His health had been good until the onset of the present condition.

Just over two years prior to admission he injured the three middle fingers of his left hand in the door of a railway carriage. They were contused and lacerated, but he continued his work and the wound healed normally. About four months later he became aware of a numb feeling in the tips of all the fingers of this hand, and clumsiness in using them, especially in manipulating small objects, as small screws and fine tools. Soon afterwards he developed a dull aching pain, not severe, extending from about the junction of the middle and lower thirds of the left thigh down to about the middle of the left calf. It was more or less constant but definitely aggravated by exercise and eased by rest. It lasted several months, gradually diminishing in severity and finally disappearing. The onset of the pain was quickly followed by the development of numbness in the area of its distribution. On touching that part it felt "numb and dead." The numbness gradually became more intense and spread upwards and downwards. At the same time he noticed a gradually progressive loss of power of this leg. The limb felt heavy and clumsy and swung outwards when he walked. He became unstable on his feet and tripped easily.

Up to six months prior to admission the condition had advanced very slowly, but from then onwards progress had been much more rapid. At that time the fingers of the right hand and the toes of the right foot had also become numb. On admission his left arm, the left half of his chest, right hand and forearm, his left leg below the middle of the thigh, and the whole of the right leg "felt numb," and his arms and legs felt weak.

There have never been sphincter, visual or auditory disturbances, and he has never had convulsions, headaches, or vertigo.

He comes from a healthy family with no history of a similar condition.

Physical examination.—He is muscular and healthy-looking. His head is inclined to the right and there is marked asymmetry of the head, face and chest as seen in the photographs (fig. 1). The neck is very thick and remarkably short, the distance from the occiput to the seventh cervical vertebral spine being only about 2 in. The muscles of the neck stand out prominently on the left, especially the upper part of the trapezius, which is firm on palpation. All the movements of the head and neck are extremely limited. The right scapula is normal in position but the left is considerably higher, and a bony projection from the inner part of its superior border can be felt under the trapezius and seen in the skiagrams. A bridge of bone, also visible in skiagrams, extends from the transverse processes of the sixth and seventh cervical vertebræ to the upper part of the vertebral border of the scapula, where it articulates with this bone. The scapula is almost fixed and permits of very little movement. Its vertebral border stands out prominently, separated from

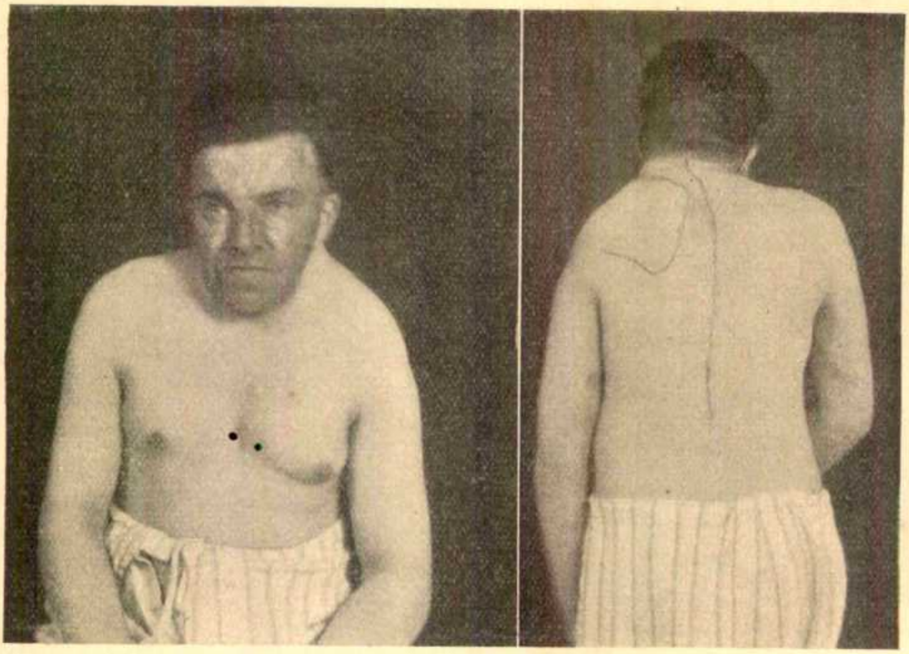

FIG. 1.—Photographs showing the deformity of the left shoulder, the shortness of the neck, the scoliosis, the tilting of the head, the asymmetry of the face and the over-development of the mammæ. The border of the scapula and the position of the vertebral spines have been marked out in ink.

the thorax. Movement of the left arm at the shoulder is normal in all directions up to the horizontal, but above this, because of the degree of immobility of the scapula, it is very limited. The right upper arm is ¾ in. less in circumference than the left, but of the same length. The forearms and hands are symmetrical and equal in size. The left leg is uniformly thinner than the right, being 1 in. less in circumference. There is no difference in length. He states that this has been so with the arm and leg since childhood.

The mammæ, especially the left, are over-developed and he has a noticeably protuberant belly. The skin over the trunk is moist and greasy, showing obvious vasomotor and pilomotor disturbance. On the ball of the right thumb there are scars of burns by cigarettes, although he had never been aware of pain and discomfort.

Speech and articulation are not disturbed and his mental functions are normal.

The retinæ and optic discs are normal. The pupils are moderate in size, but the right one is slightly larger than the left. Neither is quite circular but both are central and regular. The direct and consensual reactions to light are somewhat sluggish, especially those of the right. Both react normally on convergence. There is well sustained and regular horizontal nystagmus in both eyes on deviation to the right and left, but slightly faster on looking to the left. The left palpebral fissure is narrower than the right; this is part of the general facial asymmetry. There is no ex- or en-ophthalmos.

Motor system.—He is right-handed. The right biceps, although normal in consistence and action, is definitely smaller than the left. On the left the rhomboids, latissimus dorsi and serratus magnus are smaller than normal.

Power of certain movements is defective on both sides. Abduction of both shoulders, external rotation on the right, and external and internal rotation on the left, are weak. On the right supination and pronation, and on the left supination, are weak. The right and left long extensors of the fingers are feeble. There are no involuntary movements. Slight inco-ordination, with an error of projection, is present on the left but not on the right, in "finger—nose—finger" tests. Posture is maintanied normally. There is a noticeable increase of flexor tone, clasp-knife in type and greater on the right. Finer and alternate movements are poorly performed, especially on the right.

The intercostal, spinal and abdominal muscles are normal. There is no localized bulging of the abdominal wall on coughing, or deviation of the umbilicus on attempting to sit up.

Although the left leg is thinner than the right, there is no definite wasting of the muscles. Power is not appreciably impaired in either leg. There is marked bilateral spasticity of the clasp-knife variety. Incoördination is noticeable on both sides, but is greater on the right. Posture is normal.

Reflexes.—All the tendon-jerks are symmetrically much exaggerated. A jaw-jerk is present and there are well-marked finger-jerks on both sides. The legs are thrown into clonus even on comparatively gentle manipulation. There is well-sustained ankle-clonus on both sides. Both plantars are extensor. The upper abdominal reflexes are much reduced and the lower ones are absent.

Sensory system.—There is much disturbance and dissociation of cutaneous sensibility. Appreciation of painful stimuli is defective on the left below a line running from about two inches above the nipple to the tip of the left shoulder and then to the spinous process of the third dorsal vertebra. On the right the upper limit is defined by a line across the chest at the level of the lower border of the manubrium sterni; it curves over the top of the shoulder and runs along the root of the neck to the spinous process of the first dorsal vertebra. The analgesia is greatest on the right arm, the right side of chest, and the right leg, and least in the area of the sacral roots (fig. 2). Appreciation of heat and cold is impaired up to a slightly higher level (fig. 3). Tactile sensibility is defective below the knees only. The upper limits of the areas of the sensory disturbance do not correspond to root levels or cord segments. Vibration is only feebly appreciated on the styloids and malleoli; on the right malleolus it is hardly perceptible. Postural sensibility is grossly defective in both the upper and lower limbs, especially in the right leg, where even gross passive movements of the toes are not recognized. Two-point discrimination is defective on both palms, and form is not recognized accurately by either hand.

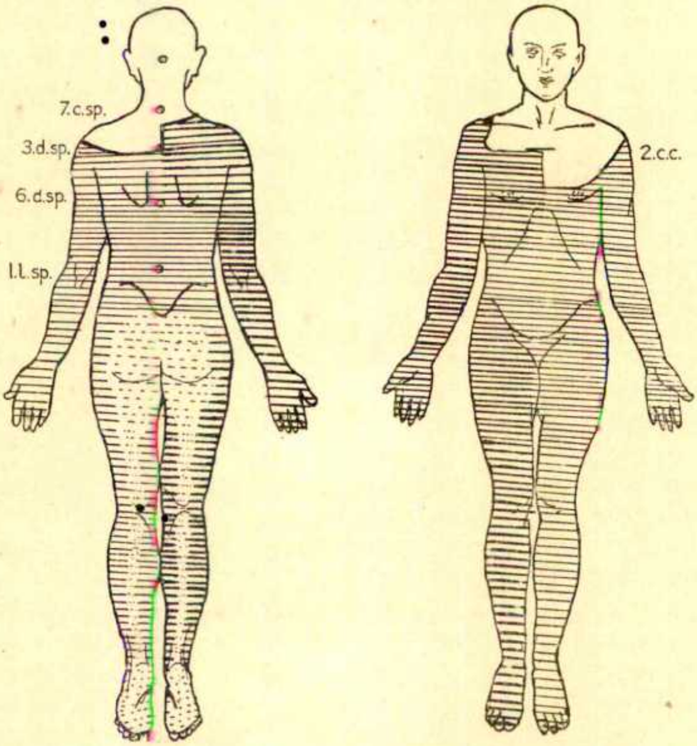

FIG. 2.—Diagram showing impairment of cutaneous pain sensibility. Shaded part indicates area where this is diminished. The degree of shading indicates the degree of impairment.

Romberg's sign is marked. His gait is slow and extremely spastic. The feet are just raised off the ground, his steps are short and he walks with a wide base. He is very unsteady and tends to fall forwards. The arms do not swing as he walks.

Nothing abnormal was found in the cardio-vascular, respiratory, alimentary and genito-urinary systems.

The cerebro-spinal fluid was not under pressure and there was no evidence of obstruction. The Wassermann reaction was negative in both his blood and cerebro-spinal fluid.

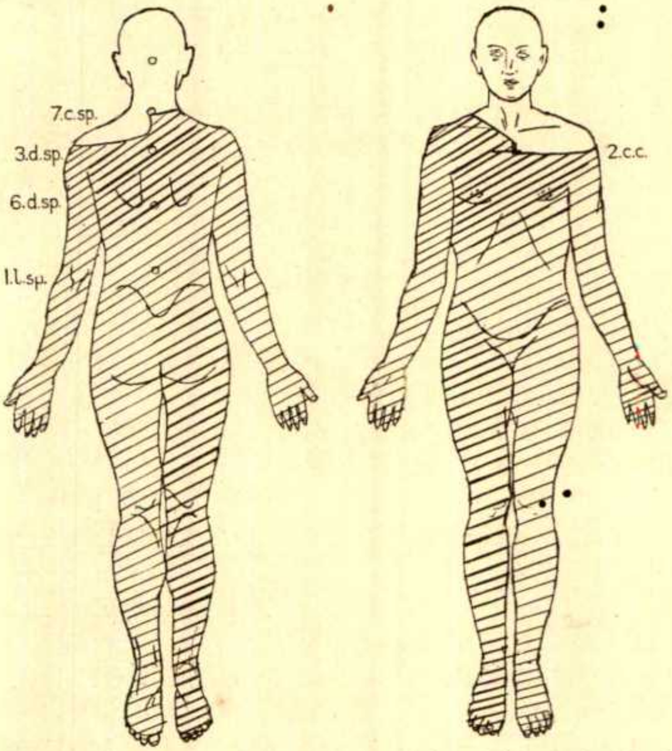

FIG. 3.—Diagram showing impairment of appreciation of heat and cold. Shaded part indicates area where this is defective. The degree of shading indicates the degree of impairment.

Comment.—Attention was first directed to that type of deformity of the shoulder present in my case by Underburg, who, in 1693, reported three cases as dislocation of the scapula. Later, Eulenburg (1863), in Germany, and Willet and Walsham (1880 and 1883) in this country, recorded similar cases. Sprengel [2], in 1891, published three cases, giving a detailed description and making a suggestion as to its ætiology. Since then many other cases have been reported.

The most conspicuous features of the deformity in this patient are the marked elevation of the left scapula, the shortness of the neck, the tilting of the head and the scoliosis. In the Sprengel deformity the scapula may be normal in size and shape, or may be malformed and irregular. The vertical measurement may be diminished with an increase of the horizontal measurement, causing it to retain a fœtal shape or to approach in form that of the scapula of some of the lower animals, e.g., the sheep. In my case, as in several others recorded [6], [7], [8], a bony bridge, curved, and roughly triangular in shape, runs from the transverse processes of the sixth and seventh cervical vertebræ to articulate at its base with the upper portion of the vertebral border of the scapula. It is probably partly responsible for the fixation of the scapula. Scoliosis, which may be very severe, and defects and anomalies of the ribs, are usually present. In my skiagrams the first three ribs of the left side are very irregular in size and shape, but this may be secondary to the scoliosis of the cervical and upper thoracic spine. Other bony malformations which have been found co-existing with the condition are cleft palate, shortness of the humerus or clavicle, or both, synostosis of the radius and ulna or absence of the radius, maldevelopment of the whole upper limb, club-foot or shortness of the femur [6], [7], [9]. Boyd [10] reported a case in which the deformity was associated with Hirschsprung's disease with intestinal obstruction.

The deformity is a congenital one, and various theories have been advanced to explain its ætiology. Sprengel [2], [9] believed it to be the result of malposition of the fœtus *in utero*. It has been observed that many of the patients were born with posterior displacement of the affected limb. The condition, however, is generally attributed to a developmental arrest. In the early embryo the scapula lies opposite the lower four cervical and the first two dorsal vertebræ. During development it gradually descends, and even at full term it occupies a higher level than it does in later life [9], [11]. Kausch [12], Hödlmoser [13] and Neumann [14] attribute this failure to descend to the abnormality of the trapezius muscle, while Rager [15] suggested that the shape of the superior border of the scapula, and especially the anterior curvature of the suprascapula, may be the cause of the arrest. Chievitz [11] believes the condition to be a reversal to a lower type, or retention in the fœtal position. Others have suggested that poliomyelitis may be a factor (Bloch).

In addition to the deformity originally described by Sprengel, there was in my case abnormality in the conformation of the vertebral column also. Owing to the abnormal position of his head and the shortness of his neck, it was difficult to obtain satisfactory skiagrams of the upper cervical vertebræ. It was, however, obvious from a series of skiagrams taken from different angles that some of the upper cervical vertebræ were absent. This has been described as the Klippel-Feil syndrome [4] [21], the essential features of which are absence or fusion of some vertebræ, or absence of some with fusion of others, scoliosis, spina bifida and abnormal distribution of the hair of the scalp. Cases have been described in which fusion of cervical vertebræ and malformation of the cranium were associated with ataxia of the Marie and Friedreich types [20].

In this case, therefore, we have two types of skeletal deformity which were originally described separately, but in many of the cases of the Sprengel deformity there have been abnormalities in the development of the vertebral column similar to those in my case and in the one recently described by Macdonald Critchley [1], and also in cases reported by others, e.g., Niederle [3], Fairbank [6] and Hibbs and Correl-Loewenstein [7]. These deformities are evidently congenital in origin and dependent on some anomalies in the development, whatever their immediate cause might be.

There can be little doubt of the nature of the neurological disturbance in my case, as all the symptoms point to syringomyelia. The character of the sensory disturbance, the slow and gradual onset of the condition and the spastic state of the limbs with paresis of the arms, are all in favour of this diagnosis. The negative Wassermann reaction in his blood and cerebro-spinal fluid excludes spinal syphilis, while the absence of any evidence of blockage, as revealed by lumbar puncture, makes a compression of the cord improbable. The possibility of intramedullary tumour has to be considered, but again, because of the absence of evidence of blockage, it is clear that the cord was not sufficiently swollen to obstruct the circulation of the cerebro-spinal fluid.

Syringomyelia is not infrequently associated with other developmental anomalies, and the view is generally held now that in many cases at least the origin of the disease must be sought in some congenital or developmental anomaly of the spinal cord.

A certain amount of importance has been given to trauma in the pathogenesis of syringomyelia [19], but the only injury which the patient received during the years preceding the onset of his symptoms entailed severe bruising of some fingers of his left hand, and this can scarcely have had an influence on the pathogenesis of the spinal disease. The fact that, although the injury was relatively severe, he was able to continue work, suggests that even at that time there was diminished sensibility to pain in his fingers.

The only case I can find in the literature comparable to my own, in which the Sprengel deformity was associated with syringomyelia, was that recently published by Macdonald Critchley [1], in which, however, the diagnosis has not been confirmed by anatomical examination.

The following is a résumé of the case described by MacDonald Critchley [1].

A man, aged 45, had since the age of 2 years a deformity of the left shoulder and neck and his left arm was weak. At the age of 30 his arms were twisted behind his back, and since then he complained of pain in his thorax and weakness of his legs.

He appeared to have scarcely any neck. The head was tilted towards his left shoulder. The right scapula lay at a higher level than the left and was rotated upwards so that the vertebral border could be felt under the trapezius, There was sharp angular scoliosis of the cervical and upper thoracic vertebræ with the convexity to the right. The angles of the ribs were more prominent on the right side, and the left half of the chest bulged in front. The left arm and leg were smaller than the right and left leg was rigid and longer than the right. The left half of the face was slightly smaller than the right and the palpebral fissures were unequal, but there was no localized wasting of muscles.

Tactile sensibility was undisturbed. The appreciation of pinprick was defective over the whole of the right leg and the right side of the trunk up to the level of the fourth thoracic segment, but the area between the eighth and the fourth thoracic segments was less involved. The appreciation of heat and cold was also impaired over the same area as pinprick. Postural sensibility was defective in the toes and ankles of both feet; vibration was not appreciated on the right external malleolus, and form was not recognized accurately in either hand.

All tendon-jerks were present but exaggerated on the left side, and both plantars were extensor.

The vertebral column appeared to show a reduction in the number of cervical vertebræ.

We may, therefore, assume that we have two conditions usually separate, but both developing on a congenital basis, combined in the case I report here, and in that described by Critchley.

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CHRONIC SUBDURAL HÆMATOMA: A STUDY OF EIGHT CASES WITH SPECIAL REFERENCE TO THE STATE OF THE PUPIL.[1]

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INTRODUCTION.

CHRONIC subdural hæmatoma is diagnosed with sufficient rarity that a review of eight cases, with special emphasis placed on accurate localizing signs, seems worthy of report. Moreover, a correct diagnosis of the site of the lesion should invariably be followed by operation and complete recovery.

A review of the literature of this subject need not be given, for it has been thoroughly covered only recently by Putnam and Cushing [1], and by Sherwood [2].

Six of the eight cases to be reported were personally observed clinically as well as at operation or autopsy, the other two were seen only at autopsy.

That chronic subdural hæmatoma occurs more frequently than middle meningeal hæmorrhage is as yet not fully appreciated. Certainly the syndrome of the former is not as well known. The eight cases to be reported were seen over a period of eighteen months, and during this period one instance of middle meningeal hæmorrhage came to my notice. Only two of the eight cases were correctly diagnosed.

In the study of the cases to follow the clinical syndrome, so clearly described by Trotter [3], has been repeatedly confirmed. Special attention, however, has also been paid to the unilateral dilatation of the pupil which has been found to correspond with the side of the lesion. The sequence of the cases is given in the order they were seen. It will be noted that with the study of each additional case, the clinical picture of chronic subdural hæmatoma became more distinct and more dependable.

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REPORT OF CASES.

Case 1 (Barnes Hospital, Unit No. 222235).—Trauma to occipital region; lucid interval[1] of ten days; headache, drowsiness, pyramidal tract signs pointing to a lesion on the right side. Operation with disclosure of a subdural hæmatoma on the right. Death the following day. Necropsy.

History: W. R., a boxer, aged 27, was admitted to Barnes Hospital on October 27, 1929, complaining of headache and drowsiness.

Ten days previous to his admission he received a blow over the occipital region during a sparring bout which stunned him for a few moments. He was not unconscious. He discontinued boxing and soon started to complain of headache which persisted and kept him awake through the night. His physician found no evidence of intracranial injury at this time. His headaches continued until thirty-six hours before entry, when he became increasingly drowsy and stuporous.

Examination: When first seen at the hospital he could only be aroused to answer "yes" or "no," and would fall back again as if asleep. Both pupils were under the influence of mydriatics. There was a palsy of the oculomotor nerve on the right, as well as a facial weakness of central type on the same side. The fundi were normal. The knee-jerks were more active on the right than on the left. Oppenheim sign was positive on the right, and ankle-clonus was obtained on the left. There were no irritative meningeal phenomena.

The temperature, pulse and urine were normal. The blood-pressure was systolic 115, and diastolic 70.

Clinical course: The patient was given 50 c.c. of 50 per cent. glucose intravenously with no apparent improvement. Six hours after entry the patient was more stuporous, more difficult to arouse, and the entire left side of the body was spastic with occasional twitchings of the left arm. His pulse dropped from 85 to 64 per minute, and during this time there was a rise of 35 points in systolic blood-pressure. The diagnosis was subdural hæmorrhage on the right side.

Operation: A right subtemporal decompression was done by Dr. Roland Klemme. The dura was tense, greyish-blue, and non-pulsating. As the dura was incised about 100 c.c. of old clotted blood spurted forth. The dura was then opened widely, and about 120 c.c. of thick clotted blood were removed, but no bleeding point could be found.

The following morning the patient was still unconscious. Lumbar puncture yielded 45 c.c. of uniformly blood-tinged fluid. Intravenous glucose was of no avail and he died that afternoon.

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[1] By the term "lucid interval," Bowen [4] means the period from the time of trauma to the onset of unconsciousness, and by the term "latent interval" the period from the time of the trauma to the onset of symptoms of intracranial pressure or cortical irritation. These terms will be used in the above sense.

Necropsy: There was no evidence of fracture of the skull. The subdural space on the right was distended with blood, causing several depressions in the brain. The cerebral veins were distended but not thrombosed. There was an area which appeared like an old laceration over the posterior part of the right occipital lobe; the hæmorrhage in part seemed to have come from a vessel deep in that region. The entire right occipital lobe was soft, cyanotic, and covered with blood. There was a marked pressure cone of the cerebellum.

Comment.—A blow over the occipital or frontal region frequently precedes the formation of a subdural hæmatoma. Indeed, it is this type of trauma which shakes the brain in a direction at right angle to the vessels entering the superior longitudinal sinus.

Although headache persisted from the start it was not until nine days following the trauma that drowsiness set in.

Transient signs of left-sided cerebral involvement were soon followed by distinct signs pointing to a lesion over the right motor area.

The findings at operation were typical, and had the patient been spared the additional complication of laceration of the brain with subsequent softening of the occipital lobe, the outcome would unquestionably have been favourable.

In this patient the pupils were under the influence of homatropine before a record of their size and reaction was made, but it will be noted that the third nerve palsy was on the side of the lesion.

Interestingly enough, Brock [5] has recently reported a similar case of chronic subdural hæmatoma in a boxer who had a dilated pupil on the affected side. In this connection it is important to note that since boxing has become a popular sport in Germany, a total number of twenty-two deaths have been reported as a result of injury sustained in the ring. In a study of these cases, Wolf [6] could obtain sufficiently reliable information in thirteen cases only. Of these, 6 or 43 per cent., died of traumatic subdural hæmatoma.

Case 2 (Barnes Hospital, Unit No. 22567).—Head injury followed by unconsciousness for two and a half hours. Latent interval of two months and ten days, followed by headache, disorientation and drowsiness. Pyramidal tract signs on the left. Negative spinal fluid. Death without operation three months after injury. Necropsy disclosure of a subdural hæmatoma on the left side.

History: P. P., an Italian miner, aged 66, entered the hospital on November 20, 1929, complaining of pain over the forehead and over the left temporal region of ten days duration. In September, 1929, while at work in a coal shaft, a large lump of coal struck the left side of his head. He was unconscious for two and a half hours, then semi-conscious for about another one and a half hours. His condition gradually improved, so that ten days following his injury he returned to work. He continued on his job as a miner for two months and ten days from the date of his injury, when headaches over the left temporal region forced him to bed. His headaches increased in severity and four days before entry he became unsteady in gait and disorientated. Weakness, drowsiness and urinary incontinence soon followed. A radiogram of the skull taken before his hospital admission was reported to have shown a fracture.

Examination: The patient was a frail Italian worker who was confused, disorientated and unable to co-operate. His pupils were equal though the left one was somewhat irregular; both reacted promptly to light. The fundi and the cranial nerves were normal. There was no demonstrable motor weakness and no sensory impairment could be determined. The deep and superficial reflexes were all present, active and equal. There was some rigidity of the neck and bilateral Kernig sign. A positive Oppenheim and a suggestive Gordon sign were found on the left side. The plantar reflexes were normal.

The urine was normal. A lumbar puncture showed clear spinal fluid under normal pressure, containing four leucocytes per cubic millimetre. No organisms were found in the spinal fluid and the Wassermann reaction was negative.

Clinical course: November 24, 1929: A visiting neurologist made the following note. "There is evidence of a lesion of the left hemisphere, which seems to be a receding process and is probably vascular in nature. Babinski is positive on the right. There is a suggestion of astereognosis on the right, although co-operation is poor."

November 27: The patient was confused, disorientated, and soiled himself. On the following day a lumbar puncture was repeated; the fluid was under slightly increased pressure. The cell-count and globulin were normal, the Wassermann and Kahn tests were negative and the colloidal gold was 1122100000.

December 2: The patient's course was steadily downhill. Stupor gradually deepened into coma and he died that night.

Necropsy: A careful search did not reveal any cranial fracture. As the dura over the left hemisphere was reflected there came into view a partially organized blood-clot adherent to the under surface of the dura which covered an area 4 × 5 cm. In addition there were 8 oz. of fairly fresh blood which appeared as if it had recently clotted. Beneath the clot the brain was depressed and yet no great change in the contour of the convolutions was noted. The convolutions of the opposite hemisphere, however, were definitely widened and compressed. Microscopical sections of the brain showed no pathological changes.

Comment.—In this patient there was a "latent interval" of two months and ten days. Once having started, his headaches were followed by disturbed gait, disorientation, drowsiness and periods of unconsciousness, all within four days. He appeared tired and sleepy. His malady did not seem serious. Finally, signs of meningeal irritation and inequality of the pupils made luetic meningitis a strong possibility, even in the face of negative spinal fluid findings. With the exception of a positive Babinski on the right and an Oppenheim on the left, no localizing signs were found over a period of twelve days' observation in the hospital. During the intervals when he seemed more alert and responsive there were no suggestions of aphasia.

The findings at autopsy were certainly out of proportion to the scanty neurological signs, thus justifying a feeling of uneasiness about encountering similar conditions in the future. Just one month later another patient came under observation which added more difficulties to our uncertain state of mind about this illness.

Case 3 (Barnes Hospital, Unit No. 2,2887).—Thrown off a horse, unconscious two hours, "latent interval" three weeks. Headaches, drowsiness, stupor, alternating pyramidal tract signs; clear spinal fluid; periods of unconsciousness. No operation; death nine weeks after injury; necropsy disclosed a bilateral subdural hæmatoma.

History: On December 18, 1929, J. S., a physician, aged 60, entered the hospital with the complaint of right-sided headache of seven days duration. He was always a rugged healthy person. On October 24, 1929, his horse stumbled and threw him. When his employees rushed to his aid he asked to be taken to his own home on the premises. Soon he lapsed into unconsciousness which lasted two hours. There was no bleeding from nose, ears or mouth. After three days in bed he began to complain of pain over the lower third of the left tibia. He managed to get about the house on crutches, but complained of increasing pain in his left leg, especially when he shifted his weight to the affected limb. Three weeks after his injury he began to complain of intermittent right-sided headache. Only moderate relief was obtained from increasing doses of "painodyne" tablets. His headaches gradually became more severe, so that by December 8, 1929 (six weeks after his injury) a roentgenogram of his skull was taken which suggested a depressed fracture of the inner table over the left temporo-occipital region. His headaches became more intense, keeping him awake at night, and finally he was brought to the hospital.

Examination: At the time of his admission he appeared well nourished, mentally alert and co-operative. He did not complain very much about his headache. There were no external signs of head injury and no percussion tenderness. The pupils were slightly irregular, equal and reacted promptly to light and accommodation. The fundi were normal. There was a very fine horizontal nystagmus in both directions. The other positive findings were some ecchymosis and tenderness over the injured area of the left leg and positive Babinski and Oppenheim signs on the right. His condition remained unchanged for the next four days. On December 23, 1929, the patient appeared rather semi-stuporous, the left eye was kept open more than the right. He could be aroused, but when left undisturbed he fell asleep very readily. The abdominal and cremasteric reflexes were absent. The Babinski and Chaddock signs were positive on both sides. A consulting neurologist made the following note: "Nystagmus in both directions, pupils small and equal, lagging of the right side of the face about the mouth, although yesterday the left side of the face seemed to be weaker. Arm reflexes were not obtained, patellar reflex on the right is difficult to obtain, the left one is active. Bilateral Babinski." The spinal fluid was normal.

December 24, 1929: A left peripheral facial weakness was observed. The bilateral Babinski persisted. A medical consultant found the lungs clear although the respirations were of Cheyne-Stokes type. He felt the condition could be accounted for by some intracranial lesion and that it was not due to any general disturbance.

December 25: The patient seemed much brighter after an infusion of 50 c.c. of 50 per cent. glucose. He was able to recognize his nurse, spoke to his relatives, but readily fell asleep when left alone. For the next five days he remained stuporous and did not respond in spite of intravenous glucose therapy at frequent intervals.

December 30: The pupils were pin-point although no narcotics or sedatives were used for five days. Respirations were of the Cheyne-Stokes type. The arms and legs were flaccid.

January 1, 1930: The patient was still stuporous and more difficult to arouse; the new findings were a definite weakness of the right arm and leg and a divergent strabismus on the left.

January 3: Stupor deepened into coma and death ensued. Repeated examinations of the urine were negative except for a trace of sugar following glucose infusions. The blood Wassermann and Kahn tests were negative. The blood-pressure: systolic, 140; diastolic, 100. Non-protein nitrogen 42 mg. per 100 c.c. of blood. Blood-sugar 116 mg. per 100 c.c. of blood. Phthalein excretion was 65 per cent. Roentgenogram of the skull showed no evidence of fracture. The pulse and temperature were normal until close to the end.

Necropsy: The calvarium was removed with ease, and shining through the dura were two greenish-blue masses, one over each hemisphere. As the dura was peeled back the bluish masses were found to be partially organized blood-clots extending over the fronto-parietal-temporal areas and in part adherent to the under surface of the dura. The hæmatoma on the right measured about 5 oz., the one on the left measured 8 oz. The underlying brain was compressed and conformed to the shape of the hæmatoma. The convolutions were not flattened, maintaining their normal configuration. The compression had taken place at the expense of the ventricular system. There was a definite membrane which enclosed these clots and closed them off from the subarachoid space. Many atheromatous plaques were noted over the basilar artery, but no cerebral thrombosis or laceration could be found. A search failed to reveal any fracture of the skull. On section of the brain there were many small hæmorrhagic areas throughout, and in the middle left portion of the pons there was one large area of fresh hæmorrhage 1 cm. in diameter, undoubtedly a terminal event.

Comment.—Here again there was an interval of three weeks between the time of the injury and the warning sign of headache. That the spinal fluid was normal is not surprising, because a hæmorrhage strictly confined to the subdural space will obviously not stain the spinal fluid. There was no suspicion of aphasia during the entire course of the illness, which can be explained on the basis that the brain makes remarkable adjustments to slowly expanding intracranial lesions.

The clinical picture in this patient varied so from morning to evening, and indeed throughout the entire duration of the illness, that no localization of the lesion could be made with any degree of certainty. The "see-saw" of neurological signs, pointing to one side then to the other, stayed the hand of the surgeon, even to the point of performing a ventriculogram. In retrospect a bilateral trephine over the temporo-parietal region, the most common site of such lesions, would have disclosed both subdural hæmatomata.

With three patients dying of this condition in three months, two undiagnosed until necropsy, it was only natural to be on guard and not to temporize. Before six more weeks had passed such an opportunity presented itself.

Case 4 (Barnes Hospital Unit, No. 23443).—Head injury while under the influence of alcohol. Lucid interval of nine days; ptosis and dilated pupil on the affected side; operation with removal of subdural clot. Recovery.

History: On February 6, 1930, M.W., a coloured female, aged 24, presented herself at the Out-patient Department of the hospital complaining of trouble with her right eye. It was found that she had a complete palsy of the third nerve on the right. The right pupil was larger than the left and fixed to light. She was admitted to the hospital on the eye service.

Her illness started during a drunken spree about nine days previous to entry when she received a blow over the right side of the head and was unconscious for ten or fifteen minutes. That night she had diplopia and the next day she vomited several times. She was troubled very little with headaches, but was concerned about poor vision in her right eye. After eight days in bed she finally came to the hospital.

Examination: In addition to the right amaurosis, a ptosis of the right eyelid and sluggish reactions of both pupils to light and accommodation were noted. The remainder of the examination was normal.

Clinical course: The morning following her entry into the hospital she seemed drowsy and by noon she was stuporous. Magnesium sulphate given by rectum did not influence her somnolence. Spinal fluid examination showed a few crenated red cells and seven leucocytes per cubic millimetre. When on the neurosurgical service she could be aroused in spite of her stupor, but her memory seemed to be poor. Several superficial bruises were noted over the left side of the trunk, the left shoulder and the hip. The right pupil remained larger than the left. The blurring of the right optic disc and the fullness and tortuosity of the veins were interpreted as early choking. The abdominal reflexes were diminished on the right. Lues was strongly suspected. On February 10, 1930, Dr. Ernest Sachs made the following note: "This patient presents a very obscure picture, the history is unreliable but there is evidence of trauma. There is a difference between the reflexes on the two sides with a tendency in favour of the involvement of the right pyramidal tract. However, the difference is so slight that more value must be attached to the lesion of the third nerve on the right. The eye grounds are normal. The patient probably has a removable clot and is to have a right subtemporal decompression and if necessary a left one also." The operation was performed by Dr. Roland Klemme. Under local novocain anæsthesia a right subtemporal decompression was performed in the usual manner. As the dura was exposed it was found under great tension, non-pulsating and with the typical blue appearance of underlying encysted blood. The dura was carefully incised and a large hæmorrhagic cyst came into view. This extended over the right cerebrum as far as could be seen with the exposure that was made. The hæmorrhagic fluid was sucked out, the clot and most of the membrane that was within reach were removed. The brain did not expand as it was expected, although it pulsated normally. No bleeding point could be discovered. The dura was not sutured and closure of the wound was performed in the usual manner except that a gutta-percha drain was inserted in order to guard against the possibility of further bleeding. While on the operating table the patient had awakened and seemed alert, orientated and co-operative. However, about seven hours later, she developed restlessness, seemed to be less alert and was somnolent.

The next morning she was comatose and the right side of her body was much weaker than the left. There was no drainage from the wound when the patient was placed on the operating table with head lowered for the purpose of re-exploring the wound. The removal of the drain was followed by the escape of about 4 oz. of bloody fluid. The patient aroused immediately, regained consciousness, and after a short interval was returned to the ward.

February 12, 1930: There was abundant drainage on the dressing. The temperature was 40·4° C. She appeared more comfortable and more alert after an ice pack. Ptosis was less marked on the right.

February 13: Palsy of the third nerve on the right was definitely clearing.

February 15: Although the temperature was normal the patient presented signs of mild meningeal irritation. This was believed to be the result of the presence of blood in the subarachnoid space.

February 17: The palsy of the third nerve on the right had completely cleared and the signs of meningeal irritation had disappeared.

February 21: The patient appeared quite sick and had fever. Twice that afternoon she vomited. There were no abnormal neurological signs. Two days later she complained of pain over her right chest and respirations became more laboured and more rapid. Signs of an abscess of the lung were found on the right, this being confirmed by roentgen ray examination. Postural drainage was instituted and continued until all of her signs cleared up.

The head wound healed by primary union, the decompression pulsated freely. She was discharged from the hospital cured on April 15, 1930, nine weeks after her admission.

Comment.—In this patient the history of injury to the head was not certain, but the slight bruises over the trunk led us to suspect the possibility of an injury to the skull.

Not infrequently a paralysis of the third nerve occurs in instances of aneurysm at the point of bifurcation of the internal carotid and in meningo-vascular syphilis. But the unexpected onset of unconsciousness and the normal spinal fluid made these unlikely. The dilated and fixed pupil on the right was in conflict with the homolateral pyramidal tract signs, but corresponded with the side of the lesion. Had we taken the attitude indicated in Dr. Sachs' note, in some of our preceding cases or in those to be reported, more recoveries would have followed. It was difficult to explain the comatose state of the patient and the weakness of the right side of her body which occurred on the morning following the operation, for it has been the consistent experience of neuro-surgeons that subdural bleeding practically never recurs once the clot has been removed. It is very likely that the state of unconsciousness which occurred on the morning following the operation resulted from the accumulation of cerebro-spinal fluid which had replaced the hæmatoma, for when this was allowed to escape consciousness promptly returned. A similar sequence of events occurred in another patient who had an extradural hæmorrhage with a tear of the dura. She regained consciousness on the operating table, but on the following morning stupor set in which cleared up shortly after the removal of the drain with the escape of bloody fluid on the dressing.

Case 5 (Bellevue Hospital).—Latent interval of one month; headache, vomiting, stupor, a dilated pupil on the left. Tumour of the brain suspected, no operation, necropsy with disclosure of a subdural hæmatoma on the left.

History: M. D., a divorced woman, aged 35, was brought to the hospital on October 3, 1930, in a comatose state. One month previously she was brought to the psychopathic ward and was discharged immediately as "not a proper case." No record of her condition at that time could be found. According to a friend she was perfectly well until four days before entry when she complained of headache and had projectile vomiting but no convulsions or visual disturbances. She had not taken any drugs or alcohol. On the morning of entry when her friend left her she seemed to be well except for her headache.

Examination: The patient was in coma, breathing regularly and deeply. She gritted her teeth continuously and was not inclined to move her left arm and left leg. There was profuse salivation. No characteristic odour to the breath could be detected. There were some traces of old ecchymosis about the right eye. The left pupil was larger than the right, both reacted sluggishly to light, and a mild external strabismus was noted on the left. The fundi were normal. The left arm was flaccid and the deep reflexes in that extremity could be elicited with considerable difficulty. The left leg moved under painful stimulation. The right abdominal reflex was diminished. The Babinski sign was positive on both sides. The urine showed a heavy trace of albumin. Blood-pressure: systolic 140, diastolic 90. Blood-sugar 120, N.P.N. 30. Only about 1 c.c. of spinal fluid was removed, for it was found to be under increased pressure. It appeared clear and colourless, but microscopically showed numerous red blood-cells and six white cells.

Clinical course: The patient was given 200 c.c. of 25 per cent. glucose intravenously. A lumbar puncture was repeated and showed a clear fluid under markedly increased pressure. The globulin and the sugar were normal. There were 120 leucocytes, 90 per cent. of which were mononuclear cells.

October 4, 1930: The patient was still comatose. There were signs of meningeal irritation. Under painful stimuli the left arm would move slightly. Abdominal reflexes were not elicited. Intravenous injection of 200 c.c. of 25 per cent. glucose was given and repeated that evening with no apparent improvement.

A neurological consultant found both pupils under the influence of homatropine. The fundi were normal, breathing was of the Cheyne-Stokes type and she was able to move all her limbs equally well. Bilateral Babinski signs were present but more marked on the left. The impression at this time was that we were dealing with a case of meningo-vascular syphilis.

October 5: At this time, because of the use of homatropine, the right pupil appeared larger than the left, both being fixed to light. There were no motor disturbances.

October 6: The temperature rose to 108° F., the respirations were 52 and the pulse was 170. The patient remained in coma and died on that day.

Necropsy: There was ecchymosis about the right eye. The right pupil was larger than the left. Three superficial bruises were found over the left arm and leg. The calvarium was removed with ease, and over the left hemisphere there was a greenish blue mass shining through the dura. As the dura was elevated there came into view a large flabby clot weighing about 150 grm. and covering almost the entire left hemisphere. The clot was encased in a thin fibrous membrane and only a small portion of it was liquefied. The remainder of the clot had the consistency of "wet blotting-paper." The underlying cortex appeared normal, but the cerebral cortex on the right was œdematous, and the convolutions were compressed and flattened. There was no evidence of a fractured skull.

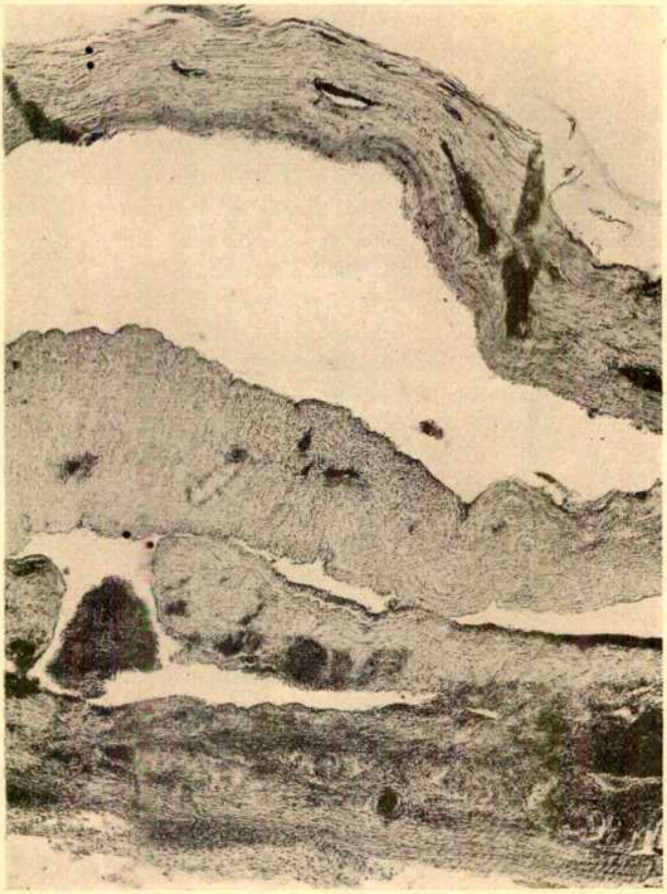

FIG. 1.

Microscopical sections from the region of the hæmatoma show outgrowths of many varying sized small vessels from the inner layer of the dura (fig. 1) which are accompanied by fibroblasts. This has the appearance of granulation tissue. There is a thicker layer of fibrous tissue nearest the under surface of the dura which is a continuation of the membrane that encased the clot. The latter can be best seen at the point of juncture of dura and clot. Sections from

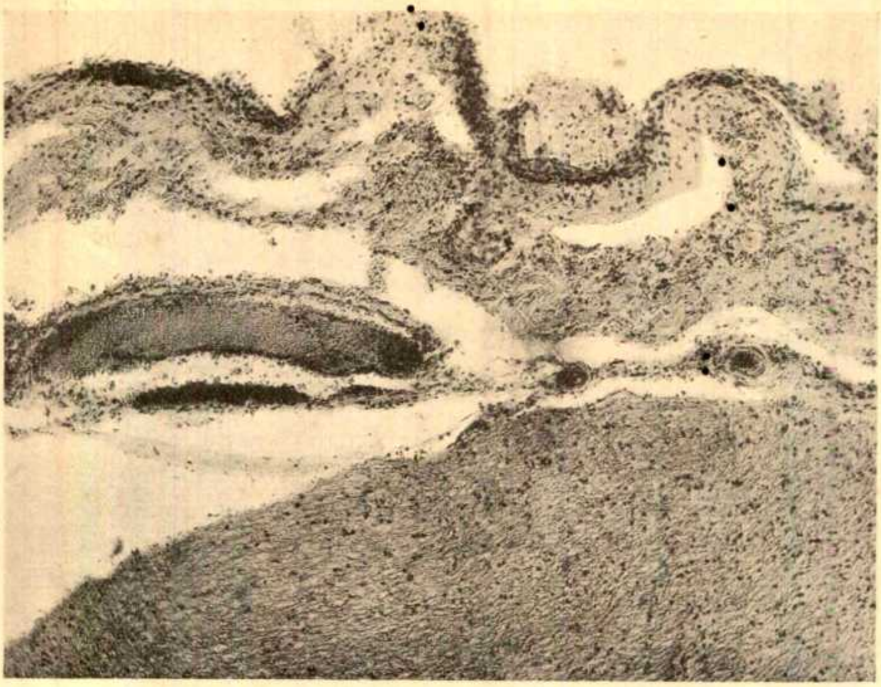

FIG. 2.

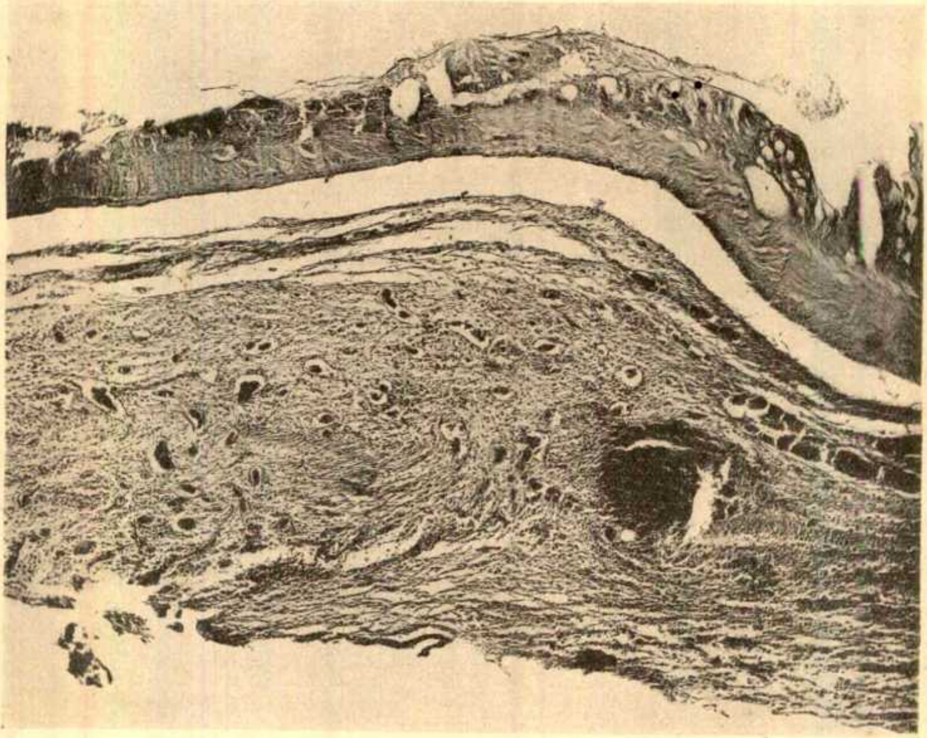

FIG. 3.

the brain underlying the clot (fig. 2) show that the subarachnoid space is compressed, and from its outer surface there is a hyperplasia of a mesothelial layer of cells which forms the inner portion of the cyst wall or neo-membrane.

Comment.—This patient presented a most difficult problem in diagnosis. The examination of the urine, blood and spinal fluid did not give any clue. There were, however, external evidences of trauma. It seems reasonably certain that her temporary admission to the psychopathic ward one month previously was not accidental and actually marks the onset of her illness. I believe she had a latent interval of one month, for the hæmatoma showed sufficient organization for a process of long standing. Again it should be noted that there were no manifestations of aphasia in spite of an extensive clot overlying the left hemisphere.

The dilated pupil on the left, observed at the time of entry, corresponded with the side of the lesion. Subsequent observations of the state of the pupils were misleading, for they were under the influence of mydriatics. The few pyramidal tract signs which were elicited were misleading, for they were homolateral to the side of the lesion. The possible causes for such misleading signs will be taken up later in greater detail.

The gross and microscopic findings are similar to those found in some of the previous cases and are in agreement with the findings of other observers who have described this type of lesion.

Case 6 (Bellevue Hospital).—Injury to the occipital region during an alcoholic state; headache, vomiting and drowsiness; lucid interval of four days. Right pupil larger than left, normal fundi. Pyramidal tract signs pointing to a lesion on the left; alternating periods of drowsiness and alertness, subsequent appearance of papillœdema. Negative exploration on the left. Death. Necropsy: disclosure of a subdural hæmatoma on the right.

History: On November 5, 1930, a 23-year old clerk entered the hospital complaining of pain over the occipital region and drowsiness.

Four days before entry when he returned home after a drinking bout he struck the back of his head against the wall. This was followed by unconciousness for about five or ten minutes and shortly afterwards by vomiting. He slept well that night but upon arising he experienced severe occipital headaches which, in addition to his drowsiness and vomiting, continued up to the time of admission

Examination: He appeared lethargic and acutely ill, complaining of severe frontal headaches. There was a tender bruised area over the left occipital region. Both pupils reacted to light but not on accommodation. The right pupil was larger than the left and there was considerable difficulty in convergence. The fundi were normal. There was slight rigidity of the neck but no

Kernig sign. Plantar stimulation produced fanning of the toes on the right but no Babinski phenomena. The urine was normal. Blood-pressure: systolic, 140; diastolic, 110; white blood-cells, 16,350 per cubic millimetre, with 83 per cent. polynuclear cells. The spinal fluid was uniformly bloody and under normal pressure.

Clinical course: That evening the patient could be aroused to answer questions. The pulse gradually became slower and the systolic pressure mounted 20 points. There was a supranuclear right facial weakness, the right grip was weaker than the left and the right knee-jerk could not be elicited. He was given 100 c.c. of 50 per cent. glucose intravenously. Two hours later his blood-pressure was 115 systolic and 100 diastolic, respirations were 16 per minute and he was less drowsy. After another hour, when aroused, he expressed the desire to go home.

Neurological examination showed in addition an internal squint of the right eye and beginning papillœdema.

Because of his restlessness he was given magnesium sulphate (25 per cent.) by rectum. About midnight the right side of his body became more spastic.

On the following morning his mental state and general condition were much improved, but three hours later he again became stuporous, his pulse became slow and his papillœdema had advanced. His pupils were under the influence of a mydriatic. The lower right facial weakness was more definite, the right arm weaker and no sensory changes could be made out. It was believed that he had a subdural or epidural hæmorrhage over the left motor area.

Operation: A subtemporal decompression was performed on the left. The dura was tense and the brain was under considerably increased intracranial pressure, but no extradural or subdural hæmorrhage was found.

The morning after operation his papillœdema was more marked, his pulse rose from 60 to 128 per minute and he had Cheyne-Stokes type of respiration. The right fundus showed choking of 4 diopters and the left 3 diopters. He gradually became more restless and more difficult to arouse. A lumbar puncture was repeated and again showed a uniformly bloody fluid. Four hours later the patient was mentally clear, orientated and spoke rationally. The right facial weakness noted in the morning was absent.

November 8: The patient was rational, fairly alert, quiet and in general appeared to be doing well. However, his papillœdema was advancing.

Second operation: An osteoplastic craniotomy was performed on the left. The dura was under great tension but no extradural or subdural pathology was found. He died the following morning.

Necropsy: This was restricted to the head. As the calvarium was removed the dura was found to be extremely tense. There was no unusual change at the site of the operation, but shining through the dura on the right side a subdural clot was seen. When the dura was opened about 50 c.c. of bloody fluid escaped and there remained about 60 c.c. of a blood-clot which was easily removed. The brain showed several deep contrecoup lacerations on the right side. About the lacerated areas, which in places were ⅜ in. in depth, and underneath the arachnoid there was considerable hæmorrhage. The left hemisphere was œdematous and showed marked convolutional flattening. Microscopical sections failed to show any other lesions except that of local hæmorrhage and œdema.

The base of the skull showed an extensive fracture beginning in the left occipital region, running along the suture line between the left parietal and occipital bones and continuing on the other side of the foramen magnum to the lower portion of the right parietal bone and ending in the squamous portion of the right temporal bone.

Comment.—The history of this patient in many respects resembles those reported above; namely trauma to the occipital region, headache, drowsiness, stupor, intermingled with periods of surprising mental alertness. It is remarkable that following the severe skull injury he was able to get about, being as active as usual. It was only upon the urgent advice of his physician that he finally came to the hospital. From his appearance, his drowsiness and stupor closely resembled natural sleep. At times his drowsiness was not unlike that of patients who have been treated with morphine.

The pyramidal tract signs again pointed to the wrong side of the lesion, but the pupil, so often disregarded, at the very outset indicated the site of the trouble. Bloody spinal fluid may mean that we have, as was found in Case 1, additional cerebral laceration, or that there is a communication between hæmatoma and the subarachnoid space.

Case 7 (Bellevue Hospital).—Comatose state. Right pupil larger than left; questionable localizing pyramidal tract signs; bloody spinal fluid, choked discs. Death without operation. Necropsy revealed a subdural hæmatoma on the right.

History: On November 4, 1930, D. S., a 63-year-old Irish labourer, found lying on the pavement in coma, was brought to the hospital. No history could be obtained.

Examination: There were no signs of any scalp wound or bleeding from any of the orifices. He had some minor lacerations of his lips but no areas of ecchymosis. The right pupil was larger than the left and both reacted promptly to light. In the evening he seemed to be sleeping quietly and perspiring profusely. There were occasional movements of the arms. The urine was normal and blood-pressure was systolic 130, diastolic 70. White blood cells numbered 16,500 per cm. Spinal fluid was uniformly bloody.

Clinical course: The next day he was mentally clear and co-operative. The right disc margins were hazy, the left arm and leg failed to respond to pin-prick and the abdominal and deep reflexes could not be elicited.

November 6: The patient kept mumbling to himself and was irrational. Roentgen ray of the skull showed no evidence of fracture.

November 7: The patient was well orientated and mentally clear, but toward the latter part of the morning he presented the picture of alcoholic delirium. Several hours later he was conscious and answered questions satisfactorily. Both pupils reacted sluggishly to light and the right disc margin still appeared hazy. The Babinski sign was negative.

November 11: The spinal fluid had an icteric tint, but contained no red blood cells.

November 14: The patient was again comatose, his pupils were dilated as a result of homatropine and both disc margins appeared blurred, the right more than the left. There was a right central facial weakness. In addition to a flaccidity of the upper right arm there was spasticity of the left arm and leg. The deep reflexes on the left were over-active. The signs and symptoms pointed to a pachymeningitis hemorrhagica interna. When seen that afternoon the patient could not be aroused, the right disc margin was hazy and the veins were markedly engorged. The right facial weakness was questionable at this time. There was a coarse tremor of both hands but no Babinski sign.

In the evening his coma deepened, the right facial weakness became more distinct, the left side of the body more spastic and the deep reflexes of the left upper extremity more active. There was a positive Babinski sign and ankle clonus on the left, but the patellar responses could not be elicited.

November 16: The fundi showed bilateral papillœdema of 3 diopters. A clear slightly xanthochromic fluid under increased pressure was obtained by lumbar puncture. Hypertonic glucose solution was given intravenously without noticeable effect.

November 19: In spite of repeated intravenous injections of hypertonic glucose solution and repeated lumbar punctures his coma deepened. His papillœdema advanced to an elevation of five diopters. The pulse, temperature and respirations all mounted, and after a stay of fifteen days in the hospital he died.

Necropsy: Externally there was no evidence of violence. The scalp was removed with ease and did not show any subcutaneous hæmatoma. When the calvarium was removed it exposed a tense dura, and over the right hemisphere a dark bluish mass could be seen shining through. As the dura was incised there spurted forth about 60 c.c. of recently clotted blood. However, a flat laminated blood-clot remained adherent to the under surface of the dura. When this was removed several pigmented and bleeding areas, having the appearance of granulation tissue, were visible.

The brain showed no laceration or sclerotic changes. The hæmatoma indented the right hemisphere, making a kind of bed for itself, being enclosed in a fine neo-membrane which stripped easily from the arachnoid. The base and vault of the skull showed no fracture.

Comment.—As in the previous patients, in this case we also had alternating periods of stupor, consciousness and coma, varying from several hours to several days. The pyramidal tract signs pointed to a lesion over the right motor area, but because they were not consistent, and because the facial weakness was not in keeping with the other signs, one hesitated in making a localizing diagnosis. The right pupil, however, was larger than the left and corresponded with the side of the lesion.

In view of the necropsy findings in Case 6 it was natural to suspect that in this case too one was dealing with a similar process. But unfortunately the sad experience of being misled by the pyramidal tract signs in the previous case prevented a similar undertaking. The necropsy findings were similar to those found in Case 6 with the exception that the brain and the skull revealed no abnormality.

Case 8 (City Hospital). Blow over the head during a drunken brawl; latent interval of one week; ptosis of the right eyelid ten days after the injury. Right pupil larger than left, indefinite pyramidal tract signs, diagnosed as acute encephalitis. Death. Necropsy disclosure of a subdural hæmatoma over the right hemisphere.

History: J.G., a porter, aged 45, entered the hospital on December 4, 1930, complaining of soreness all over the body, especially between the shoulders, generalized weakness, headache, ptosis of the right eyelid, and a watery discharge from the right eye. Twenty years previously he sustained a fractured skull, followed by complete recovery.

It was learned from his wife that for two weeks he had been drinking heavily, and that during one of his " drunks " he either fell or was in a fight, and received several severe blows over the head and body.

For a week previous to his admission he complained of fronto-occipital headaches, and on several occasions, usually in the morning, vomited forcefully. Ptosis of the right eyelid came on suddenly four days before entry, this being accompanied by a watery discharge from the eye.

Examination: On admission he was lying quietly in bed, but was rather drowsy. There were some abrasions over the right eye and forehead, and a hæmatoma over the right frontal region. An old scar about 1 in. long was found over the left occipital region. There was a ptosis of the right eyelid and the conjunctiva on that side was injected. The right pupil was larger than the left, and both reacted to light and accommodation. The fundi were normal. The deep reflexes were exaggerated; a Babinski sign on the right was equivocal, and ankle clonus was poorly sustained on the same side. The urine was negative, white blood-cells numbered 9,000 per c.mm The blood Wassermann and Kahn tests were negative. On two different occasions the blood-urea nitrogen was 21 mg. and 18 mg. per 100 c.c. of blood. A Roentgen ray of the skull revealed an old oval defect over the region of the lambda.

Clinical course. December 8, 1930: The patient was sleeping most of the time and perspiring profusely. When aroused, he seemed dull and listless. From time to time he tried to get out of bed. Lumbar puncture that morning showed clear spinal fluid, four lymphocytes, no globulin, and a trace of sugar. The Wassermann and Kahn reaction and culture of the spinal fluid were all reported negative. The colloidal gold curve was 0011111100. Toward the evening he became more lethargic; had a coarse tremor of all the extremities and manifested generalized muscular spasticity. It was thought that he had acute encephalitis. Cisternal puncture was done and the fluid was found to be under slightly increased pressure, but otherwise normal.

December 10: He was given 250 c.c. of 25 per cent. glucose intravenously, which had no effect on his lethargic state. Next day the temperature rose to 102° F., and he became incontinent. The following day he was very weak, dull, perspiring greatly, and taking very little nourishment. His temperature rose to 105·2° F., and he died.

Necropsy: When the calvarium was removed it became evident that there was a subdural hæmatoma on the right. The outer surface of the dura appeared pigmented, and there were some golden specks over the involved area. After the removal of about 100 c.c. of dark red clotted blood from underneath the dura, there came into view some firm dark-red clots which were adherent to the under surface of the dura and could be shelled off fairly easily. The clot ended abruptly, and a fine membrane could be seen running from the edge of the clot to the arachnoid. The arachnoid over the right hemisphere was reddish, and over the outer surface of the occipital region was a small dark area which appeared like a ruptured vein. The right hemisphere was somewhat smaller than the left, and the cortical convolutions of the left hemisphere were flattened. There was also a diffusion of blood underneath the arachnoid of the left parietal region.

On section the brain showed no lesions. Except for an old healed fracture over the left occipital region the skull was perfectly normal.

Comment.—The history and sequence of events in this case, with the exception of a previous operation, is almost identical with Case 4. In both there was a head injury during an alcoholic spree, an interval of ten days with headache and vomiting, followed by a sudden onset of an oculomotor paralysis on the affected side, drowsiness and coma. Fluid obtained from the lumbar region and also from the cisterna magna gave no indication of the intracranial hæmorrhage and again the fundi failed to show evidence of increased intracranial tension. That the patient was thought to have acute encephalitis is not surprising, for indeed it closely simulates chronic subdural hæmatoma, with but one exception, a history of trauma.

It is noteworthy, however, that the ptosis and the dilated pupil corresponded with the side of the lesion.

SUMMARY OF CASES.

Analysis of the cases brings out several interesting and instructive features about chronic subdural hæmatoma. The ages in this small group varied from 23 to 66 years, the average being 43 years. This condition, however, occurs not only in adults but also in infants, most frequently during their first year of life, as was shown by Sherwood [2].

There were six males and two females. The lesion was unilateral in seven cases and bilateral in one. All had either a history or evidence of trauma, or both. The interval from the trauma to the onset of the first symptom varied considerably. In Case 1 the patient complained of headaches immediately following the blow on the head, while in Case 2 the patient remained free from symptoms for two months and ten days, during which time he was able to carry on his work as a miner. The most prominent symptoms during the lucid interval were headache, drowsiness and vomiting. Objectively, lethargy resembling natural sleep and the alternating periods of alertness and somnolence were most characteristic.

In five of the eight cases the fundi were normal throughout the entire course of the illness; in one the disc margin was hazy on the affected side and in two instances changes in the fundi progressed to advanced papillœdema. The spinal fluid was perfectly clear and normal in five cases and bloody in two cases. In one case (Case 1) lumbar puncture was not done previous to operation. In five cases the pyramidal tract signs were misleading, indicating the wrong side of the lesion; in two instances they fitted in with the other findings and indicated the correct side, and in the patient who had alternating pyramidal tract signs, necropsy showed bilateral subdural hæmatoma. Only one patient had a fractured skull. In all the cases laboratory studies of the urine, Wassermann and blood were normal. In four instances there was a history of alcoholism.

The correct interpretation of the pupillary changes would have been most valuable, for in five cases a dilated pupil was found on the affected side and in one patient a third-nerve palsy was observed on the side corresponding with the lesion, but no note was made about the size of the pupils. In two cases there was a slight irregularity of the pupils but no inequality. One of these patients had bilateral subdural hæmatoma.

Only three patients were subjected to operation and of these one recovered. In another, the diagnosis was correct but the patient had additional laceration of the brain, and in the third the lesion was wrongly localized. Those who were not subjected to operation died.

Anatomical considerations.—The relationships of the subdural space are well known. Under normal conditions this space is only a potential one. It is enclosed by the under surface of the dura and the outer layer of the arachnoid, contains no fluid and is lubricated by the moisture of its two enclosing surfaces. The subdural space does not communicate with the arachnoid space and as far as is known has no absorbing power. Cerebral veins, being relatively fixed at the superior longitudinal sinus and cerebral cortex, are least supported in their course through the subdural space. Suspended within the skull by various folds of dura the brain has its greatest play in the antero-posterior direction and practically no play in a lateral direction. These anatomical considerations will help explain some of the processes that take place.

Ætiological factors.—Since the description in 1857 by Virchow [7] [16] of the condition which he named Pachymeningitis hemorrhagica interna, there has been considerable controversy as to its ætiology and mechanism. With minor variations the findings in chronic subdural hæmatoma are identical with those found in pachymeningitis interna. Virchow put forth the theory that in the insane, in chronic alcoholics, and at times in syphilitics, the dura becomes chronically inflamed, as a result of which there is a pouring out of fibrin and blood-tinged fluid on its under surface. In an attempt to organize this exudative material numerous capillaries sprout from the under surface of the dura with the formation of a granulating surface. When the original circumstances that led to the previous bleeding repeat themselves, or possibly without obvious cause, spontaneous successive bleeding occurs from this surface. The hæmorrhage in turn becomes organized, with the formation of various laminated layers of healed granulation tissue.

Virchow's view of the ætiology of this condition did not remain unchallenged, and since then numerous attempts by various workers, Kremiansky [8], Kassemeyer [9], Rosenberg [10] and others, were directed in search of the direct cause. Notably among these workers has been Barret [11], who carried out under most aseptic precautions bacteriological studies in twenty-three such cases and with one exception, probably an accidental contamination, the results were invariably negative. In eight instances, under aseptic conditions he transplanted portions of the subdural membrane into the subdural space of cats and dogs with entirely negative results as far as the production of a progressive hæmorrhagic process comparable to that occurring in man was concerned. Various chemical studies did not offer a satisfactory explanation. Those who held Virchow's view that pachymeningitis hæmorrhagica interna was the result of a generalized disease process had difficulty in explaining the localized nature of the lesions, the predilection for areas over the cerebral hemispheres, and the proximity of the lesion to the superior longitudinal sinus. Recently trauma as an ætiological factor has received experimental as well as clinical confirmation.

In 1872 Sperling [12] injected blood into the subdural space of dogs and found that organization began within a week and that membrane formation was found after three weeks. He then carried out similar experiments, using defibrinated blood, and did not find any membrane formation, which led him to the conclusion that organization was the result of fibrin irritating the dura. Microscopically the findings corresponded in all points with those found in pachymeningitis hæmorrhagica interna as originally described by Virchow. He then injected various irritating substances, such as dilute solutions of tincture of iodine, sodium chloride and acetic acid, into the subdural space and obtained negative results.

A similar series of experiments were reported by Spiller [13] in 1899. By nicking the superior longitudinal sinus in cats and dogs sufficiently to produce subdural hæmorrhage and by sacrificing the animals at intervals from six hours to five weeks, he was able to study the various steps in the formation of chronic subdural hæmatoma. He came to the following conclusions: (1) that evidence of new membrane formation was quite distinct after five days; (2) that organization begins nearest the dura; (3) that after five weeks the membrane is distinctly formed; and (4) that subdural hæmorrhage may be one of the causes of the formation of a subdural membrane. Experiments in which he painted the under surface of the dura with hydrochloric acid showed no evidence of membrane formation even after seven weeks.

In a recent analysis of forty-two cases of chronic subdural hæmatoma collected from the literature, Jelsma [14] found that only 2 per cent. failed to give a history of trauma. Indeed, the injury to the head may be so trivial that the patient fails to mention it, and in some instances the story of a head injury is first elicited after operation. In only 25 per cent. of these cases was the injury sufficient to produce unconsciousness. Of the eight cases in this review, seven had a definite injury to the head, and although in one case a history of injury could not be ascertained it seemed very probable. Unconsciousness following the injury was questionable in 50 per cent. of the cases, in the remaining it varied from five minutes to two and a half hours.

One is inclined to agree with Trotter [3] that the rôle played by trauma in the formation of chronic subdural hæmatoma is often discounted, particularly so in individuals found in insane asylums, in those who are under the influence of alcohol, and in luetics with mental changes.

The notable increase in the number of reported cases of chronic subdural hæmatoma in Germany since boxing has become so popular points very strikingly toward trauma as the ætiological factor.

It would seem then from the above studies that chronic subdural hæmatoma is a result of trauma to the head which displaces the brain in an antero-posterior direction with a resulting tear of one or more of the cerebral veins as they enter the superior longitudinal sinus and with subsequent bleeding into the subdural space.

THE PATHOLOGY.

The hæmatoma is larger in the antero-posterior diameter and may vary greatly in size, extent and consistency. In over 50 per cent. of the cases the hæmatoma contains liquefied material having the appearance of blood-stained serum. The main part of the clot has the consistency of wet blotting-paper, but the portion of the clot nearest the under surface of the dura is more tense, strips with difficulty and after its removal exposes a reddish granulating area which bleeds easily. With two possible exceptions all reported cases of chronic subdural hæmatoma have been confined to the cerebral hemispheres [15].

Microscopically (figs. 1, 2 and 3) small capillaries are found anastomosing with each other, supported by a connective tissue framework which becomes thick as it approaches the dura. The walls of the vessels are rather thin and friable and in places consist only of large blood-containing spaces lined by endothelial cells. These spaces arise from the inner and more vascular part of the dura in an effort to organize the blood-clot. There are no blood-vessels in the arachnoid, and the only response made by this structure is a proliferation of a thin layer of mesothelial cells. It seems reasonably certain that the clot comes first and the organizing process is a response on the part of the under surface of the dura.

The bleeding in chronic subdural hæmatoma is from a venous channel and is therefore slow, intermittent and variable. Invariably the rupture is in a vein entering the superior longitudinal sinus and the oozing that follows slowly dissects its way in the subdural space and if strictly confined to this space will not give any evidence of hæmorrhage in the spinal fluid. A small tear in the arachnoid will allow the escape of blood into the subarachnoid space, but this leak may soon seal itself and the fluid obtained from the spinal canal may be first xanthochromic, then clear and finally normal. The hæmatoma forming slowly over a period of days, weeks and months, acts like a growing sponge, displacing the brain tissue slowly and making a bed for itself [17]. The cerebral hemisphere on the side of the hæmatoma is smaller and usually compressed downward and inward. The opposite hemisphere is as a rule larger, more œdematous, and because it is pressed against the resisting cranial vault the convolutions become flattened and widened. The ventricular system is displaced away from the lesion and results in distortion of the size and shape of both ventricles.

Oozing from a cerebral vein will be favoured by variations in intracranial pressure, especially when that pressure falls as a result of dehydrating measures. When, however, the cyst wall has fully formed and hæmorrhage takes place within the cyst, the increased tension in the non-yielding structure will cause headache, vomiting and drowsiness. As the clot retracts and partial organization takes place, the intracranial tension readjusts itself and the patient becomes more alert and at times fully orientated. With the recurrence of the hæmorrhage the stupor and coma return.

That bilateral hæmatoma occurs in one-half to one-third of all cases, as believed by Trotter [3], is not so certain. Of ten cases reported by Cushing and Putnam only one had bilateral hæmatoma; in the series of forty-two cases by Jelsma [14], which included the above number, only two had the lesion on both sides. In all of the seven cases reported by Rand [18], the lesion was found to be unilateral. Among the eight cases reported here, bilateral hæmatoma occurred only once. The incidence of bilateral subdural hæmatoma is probably closer to 10 per cent.

For this reason it is important to localize the side of the lesion, keeping in mind, however, that such may be found on both sides, but not as frequently as previously supposed. Close observation of the changing state of the pupils in these patients will yield valuable information as to side involved.

The Pupils.

There still is variance of opinion about the pupillary changes in patients with cerebral injuries. This is not surprising when we realize that the size and the response of the pupils change frequently following trauma to the head. A careful study of Macewen's article [19] will enable one to understand better the pupillary signs during various states of shock and more particularly in head injuries. This article clearly illustrates that the size and the response of the pupil depends upon the degree of pressure which inhibits cerebral function.

Macewen tabulates the phenomena observed in his case into four phases, which are dependent upon the degree of functional disturbance of the cerebrum.

Pressure	Action on the brain	Effect on the pupil
1. Very severe	Function almost in abeyance	Stabile mydriasis
2. Removal of pressure	Restoration of function	Normal and active
3. Slight	Interruption of function	Contracted and sluggish
4. Very severe	Suspending of function ending in abolition	Stabile mydriasis

We see then that pupillary changes particularly in head injuries are transitory and only by careful and repeated observations will reliable and dependable information be forthcoming. During the irritative state, when one half of the cerebrum has had its functions interfered with, the pupil on the side of the lesion may well be smaller than on the non-affected side, but when the function of one half of the cerebrum is totally suspended then the pupil on the affected side is dilated and fixed.

From the study of the eight cases it would seem very likely that the third nerve in its course may easily be influenced by variations in intracranial pressure, as a result of which frequent pupillary changes are encountered. This nerve is likely to suffer from pressure as it crosses the sharp edge of the greater wing of the sphenoid. Pressure transmitted downward and inward, as is so often the case in subdural hæmatoma, will readily affect the behaviour by influencing the activity of the third nerve. Ptosis of the eyelid accompanying the dilated pupil would argue in favour of such a mechanism. During the early phase pressure will cause irritation of the third nerve and will result in a small pupil on the corresponding side; the pupil on the opposite side, however, will be normal in size and respond promptly to light and accommodation.

Pupillary changes give evidence of increasing pressure in cerebral trauma long before the appearance of papillœdema. In a good number of instances of cerebral trauma the dilated pupil may be the only localizing sign. As has been pointed out by Holman and Scott [20], and by Rand [21], the dilated pupil is of greater significance than a hemiparesis or bleeding from the opposite ear. That a hemiparesis has led to a negative exploration has been the experience of many neurosurgeons. In some cases one is unable to assign any cause for such misleading signs.

MISLEADING PYRAMIDAL TRACT SIGNS.

The finding of a lesion on the side homolateral with the disturbed pyramidal tract signs suggests that there was either an error in observation or a fault in interpretation. The explanation for this inconsistency is rather to be found in the morbid changes affecting the nervous system.

Misleading pyramidal tract signs have been accounted for in three ways.

(1) A study by Kernohan and Woltman [22] has shown that in those instances in which the pyramidal tract signs were misleading a distinct notch was found in the crus on the side contralateral to the lesion, at the point where it impinges against the incisura tentorii, thereby giving homolateral pyramidal tract disturbances.

(2) Then again such misleading signs have been attributed to the dilatation of the lateral ventricle on the side opposite the lesion. This can hardly be accepted for unilateral dilatation of a lateral ventricle is of frequent pathological occurrence, yet it is sometimes associated with pyramidal tract disturbances as a result of such dilatation.

(3) Finally, the most plausible explanation is that in the gradual and slow formation of the hæmatoma the underlying cerebral substance is steadily pushed away from the side of the lesion. The affected hemisphere is shrunken, but the convolutions still maintain their normal configuration. The opposite hemisphere on the other hand is much larger, more œdematous, and the convolutions flattened and compressed. Such findings have been consistent in five of the cases reported here which exhibited misleading pyramidal tract signs. Similar observations were also made by Vance [23]. It would appear then that the motor area of the cerebral hemisphere opposite the side of the lesion is the first to suffer as it is being pressed against the unyielding cranial vault. With the variations in intracranial pressure (resulting from the organization of the blood-clot, or from the repeated venous bleeding

into the blood-cyst) which are sometimes initiated by dehydrating measures, there occur not only fluctuations in the state of consciousness, but also changes in the pyramidal tract signs.

DIAGNOSIS.

The diagnosis of chronic subdural hæmatoma is not easy. Not infrequently there is the added difficulty of patients entering the hospital either in a state of coma, or so drowsy and stuporous as to make the history unobtainable or unreliable. In such cases a history of trauma may be sometimes obtained only after the operation when the patient has regained consciousness.

A history of mild trauma followed after a latent interval of several days, weeks or months, by headaches, vomiting and drowsiness should make one suspicious of a subdural hæmatoma. The latent interval may be of surprising duration, as for example the case reported by Buss [24] of bilateral subdural hæmatoma, which occurred three and one half years after the injury, and one and a half years after the onset of symptoms. That a patient may be able to carry on his usual occupation for a considerable period following his injury was observed in Case 2.

One of the most characteristic signs is the peculiar lethargic state of these patients, with alternating periods from stupor, drowsiness and coma, to consciousness within twenty-four hours or even less. Curiously enough the condition does not impress itself as being grave, and one hesitates to advise operation on so few signs. At times the patient appears as if he were naturally asleep or under the influence of a narcotic such as morphine. It is well to remember that this condition may readily be mistaken for acute encephalitis.

At times the diagnosis can only be made by exclusion and exploration. Chronic subdural hæmatoma should be seriously considered among the possibilities in the study of a patient in coma. Cerebral abscess and tumour may be most difficult to exclude. The alternating lethargic state is probably the most reliable finding in making the diagnosis. Studies of the spinal fluid and repeated observations of the fundi are often of little aid. The presence of a dilated pupil will invariably point to the affected side no matter what pyramidal tract disturbances may be present.

As a diagnostic procedure in difficult cases, trephining over the temporo-parietal region seems justifiable. The greenish-blue discoloration under the dura is unmistakable. One must not be misled by the absence of aphasia, for hæmatomas of surprising size covering almost the entire left hemisphere have been found in right-handed individuals without the slightest evidence of speech disturbance during the lucid intervals.

TREATMENT.

Once the hæmatoma has formed it is most unlikely that spontaneous recovery will take place. Operation should be performed without delay.

This will vary with the condition of the patient. In instances where one has kept close watch of the variations in the size of the pupils, uninfluenced by homatropine or morphine, a trephine should be performed over the temporo-parietal region on the side showing a dilated pupil. The trephine can be so placed that if the patient's condition permits, one can proceed to do an osteoplastic craniotomy, or enlarge the trephine to approach a subtemporal decompression. With the aid of the sucker the entire clot and the greater part of the membrane can be removed through a subtemporal approach. Bilateral openings over the temporo-parietal region are advocated by most authors because of the high incidence of bilateral hæmatomata. There is also the danger that the removal of one hæmatoma will start up bleeding in the other.

It would seem wiser to inspect first the side that exhibits a unilateral dilatation of the pupil. If no evidence of a subdural hæmatoma is found, then the other side should be investigated, but in patients with no inequality of the pupils both sides should be inspected even if a hæmatoma has been found on one side. Bilateral operation is preferable to ventriculography because it is less upsetting to the patient and in instances where the hæmatoma is on both sides the ventricles are in the main collapsed and great difficulty is encountered. Ventriculograms under such circumstances are often unsatisfactory.

The clot should be removed completely and as much of the membrane as will come with it. It has been the consistent experience of those who have operated on these patients that subdural bleeding practically does not recur and that there is no fear in closing the wound without drainage. As might be expected, hypertonic solutions of glucose or saline given intravenously have been of little avail; on the contrary they seem to favour recurrent venous bleeding. As a general rule the patient regains consciousness shortly after the removal of the clot. Failure to react promptly means that the patient has either additional cerebral laceration or a hæmatoma on the other side.

The two post-operative complications to be feared in this condition are cerebral œdema, which has been emphasized by Sachs [25], and extradural hæmorrhage which may follow any craniotomy, particularly when there is little or no increased intracranial tension at the time of operation.

PROGNOSIS.

If in addition to a subdural hæmatoma there is cerebral laceration or subarachnoid hæmorrhage the outlook is very grave. The operation, if done early enough, will usually be followed by recovery. Of the forty-two cases referred to, 77 per cent. were operated upon and of these 83 per cent. recovered.

SUMMARY AND CONCLUSIONS.

(1) A study of eight cases of chronic subdural hæmatoma shows that this condition is frequently unrecognized despite the fact that it occurs more often than middle meningeal hæmorrhage.

(2) Experimental and clinical data show that trauma, often trivial, is the important ætiological factor.

(3) A rupture of an unsupported cerebral vein as it enters the superior longitudinal sinus will most often follow a blow over the occipital or frontal regions.

(4) The surprising latent period in the great number of cases can best be explained by slow and intermittent venous bleeding into the subdural space.

(5) The diagnosis of chronic subdural hæmatoma is based on a history of trauma, which, after a latent interval, is followed by the insidious onset of headache, drowsiness, vomiting and coma.

(6) The most characteristic clinical symptom of chronic subdural hæmatoma is a peculiar lethargic state which seems to alternate from drowsiness to coma, with periods of alertness and surprising response occurring within twenty-four hours or several days.

(7) Misleading pyramidal tract signs have been noted frequently in cases with chronic subdural hæmatoma. A dilated and fixed pupil on one side, even in the presence of a homolateral paresis or bleeding from the opposite ear, points to a lesion on the same side.

(8) In seven of the eight cases reported a unilateral lesion was present, and in one the hæmatoma was found on both sides. It is believed that in instances where there is a unilaterally dilated pupil, an opening should be made first on this side, but if inequality of the pupils

has not been observed a bilateral trephine should be done simultaneously even though a hæmatoma has been disclosed on one side.

(9) The term chronic subdural hæmatoma is preferable to pachymeningitis hæmorrhagica interna. The latter should be restricted to those instances in which the subdural bleeding has resulted from causes other than trauma.

I wish to take this opportunity of thanking Dr. Ernest Sachs and Dr. Foster Kennedy for their kindness and assistance in the study of these cases.

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LATERAL SYNDROME OF THE MEDULLA.

(OCCLUSION OF THE POSTERIOR INFERIOR CEREBELLAR ARTERY. VASCULAR LESIONS OF THE HIND-BRAIN).[1]

BY A. GREIG ANDERSON, R. D. LOCKHART, AND W. CLARK SOUTER.

THE fertility of such cases of thrombosis of the posterior inferior cerebellar artery as a source of information regarding the retro-olivary region cannot be overestimated. As the anatomical, physiological and clinical significance of certain features is still unknown, this case is added to the literature in the hope that the variation of its details and the discussion of its problems may extend the knowledge, or at least indicate the obscurity, of certain aspects not dealt with in the publications consulted.

Similar cases were described by Senator [1], 1881, while the most recent accounts are by Thompson [2], 1929, Merritt and Findland [3], and Pines and Gilinsky [4], 1930. Good bibliographies may be consulted in the articles by Thompson [2], Merritt and Findland [3], and also in the work of Stopford [5].

J. T., a labouring man, aged 62, while at dinner on February 11, 1931, was seized with a sudden attack of giddiness and found he could no longer swallow.

He attended the Ear, Nose and Throat Department of the Royal Infirmary on the following day, walking half a mile to hospital, where he was seen by Dr. H. Peterkin, who reported as follows: "Much froth behind arytenoids and in piriform fossæ: an attempt to swallow resulted in laryngeal spasm."

He was admitted to the medical wards on the same day.

Clinical examination: The pupils are unequal, the left being much greater than the right. The left pupil reacts to light directly and consensually and on convergence. The right pupil reacts feebly to both light and convergence. The right palpebral fissure is narrower than the left. There is no diplopia or nystagmus. The ocular movements are full in all directions.

There is no subjective sensation of pain in the face. The sensibility of the corneæ to cotton wool is equal. The sensation of the face and auricle as tested to cotton wool and pin prick is equal on the two sides. Sensation of the tongue, gums, tonsils, palate and posterior wall of pharynx as tested to pin-prick is normal.

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[1] From the Anatomy Department, University of Aberdeen.

The temporal and masseter muscles contract equally. The facial muscles contract equally on the two sides.

Hearing is equal on the two sides.

On phonation the palate moves upwards and to the left. The sterno-mastoids contract equally. The tongue is protruded straight. On subsequent examination this varied, the tongue being protruded a little to the right.

There is complete inability to swallow solids or fluids. There is frequent cough and expectoration of mucus. With attempts to swallow, the hyoid bone and thyroid cartilage move strongly, and no regurgitation occurs through the nose. The larynx is not affected.

There is no motor paralysis of the limbs or trunk.

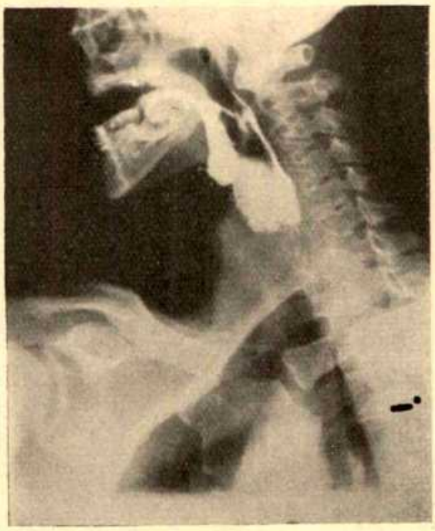


FIG. 1.

The reflexes of the arms are feeble but equal on the two sides. The upper and lower abdominal reflexes are equal, but the cremaster responses are absent. The left knee-jerk is greater than the right, as is also the left ankle-jerk. The left plantar response is extensor, the right flexor.

Sensation in the upper limbs as tested to the usual modes, cotton wool, pin prick, heat and cold, vibration and passive movement, is normal. In the lower limbs light touch with cotton wool is appreciated equally on both sides. Pain sensibility is defective on the left limb and on the left side of the trunk up to the umbilicus. Heat and cold are not distinguished in this area. Vibration sensibility and the sense of passive movement are not impaired.

There is no disturbance of co-ordination. Gait and station are normal.

There is very little alteration in the tonus of his limbs; possibly it is a little increased in the left arm.

At subsequent examination the sense of taste, always a difficult and delicate problem, was found to be defective on the right side of the tongue, and one could pass the finger over the fauces and epiglottis without producing nausea. An opaque meal examination shows a complete hold up at the upper end of the œsophagus (fig. 1).

To Dr. W. Clark Souter we are indebted for the careful reports on the patient's eyes.

March 25, 1931. The right pupil measured 2·5 mm., the left 4 mm.

The right palpebral fissure is narrower. There is no enophthalmos. The right pupil acts feebly and equally to direct light and consensually; the left acts fairly well to light both ways. The right dilates not at all in the dark but the left dilates well in the dark. Both pupils act on convergence.

March 30: The effect of 3 per cent. cocaine hydrochloride on the eyes as regards size of pupils and height of palpebral fissure was estimated, a drop being applied to each eye at 9.45 a.m., and again at 10.45 a.m.

March 31: Ophthalmoscopic examination after homatropin and cocaine. Pupils dilated and circular, both optic discs have a whitish tint, with soft edges but without signs of previous neuritis; arteries of fair calibre with, here and there, a suggestion of some compression of the veins at the crossings, but no high degree of vascular degeneration.

On the right some superficial choroidal atrophy as an angular patch at the yellow spot area and to its nasal side, with three soft yellow spots at the outer side of that area.

On the left a sharply defined angular area of choroidal atrophy with three pigment dots just over the yellow spot area, and here some white tissue lies along the wall of a vessel that comes down from the superior temporal vessels, probably an artery which has thrombosed. The rest of the fundi seems normal.

It thus appears that in this case the right palpebral fissure and the right pupil were smaller than the left, but that under the stimulus of cocaine the right palpebral fissure opened up through 1·5 mm., whilst the left opened up through 2 mm., and further, that the right pupil opened up through 1·5 mm., whilst the left opened up 3·25 mm., the dilatation of the right pupil reaching its maximum in 2¾ hours, that of the left in 1½ hours. Practically no dilatation took place in the right pupil at 1½ hours, whereas the left had already begun to dilate at the end of the first 15 minutes (fig. 2).

The patient showed signs of cardiovascular degeneration with fibrillation of the heart. The Wassermann reaction of the blood-serum was negative.

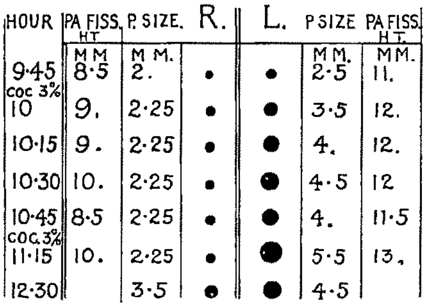
The paralysis of deglutition persisted for some three weeks and then gradually subsided.

The patient was seen again some five months later, on July 27. He then stated that he felt perfectly well, and that he had no difficulty in swallowing, but that he had a curious sensation of warmth in the left leg from the knee downwards.

The pupils were still unequal, the left greater than the right, but the palpebral fissures appeared to be equal. The palate still moved up to the left. Taste was defective on the right side of the tongue. The nausea reflex had returned, i.e., stimulation of the pharynx with the finger now caused vomiting. The sensation of the left limb and trunk up to the umbilicus to pain and temperature was still defective. The left plantar response was extensor.

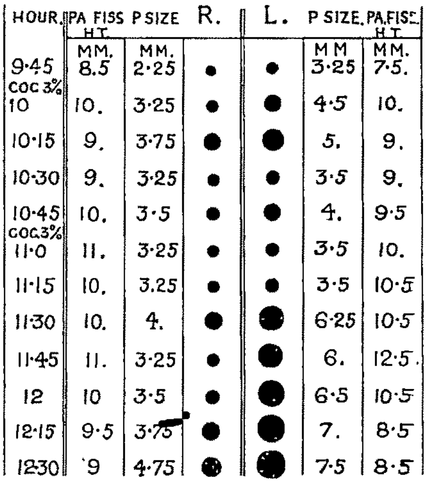
Dr. W. Clark Souter again examined the eyes with the following result:—

August 16: Now that the general clinical features had materially improved, a parallel series of observations was made to indicate the effect of cocaine on the palpebral fissure and pupil.



HOUR	PA FISS. HT.	P. SIZE.	R.	L.	P SIZE	PA FISS. HT.
	MM	MM.			MM.	MM.
9·45	8·5	2.	●	●	2·5	11.
coc 3% 10	9.	2·25	●	●	3·5	12.
10·15	9.	2·25	●	●	4.	12.
10·30	10.	2·25	●	●	4·5	12
10·45	8·5	2·25	●	●	4.	11·5
coc. 3% 11·15	10.	2·25	●	●	5·5	13.
12·30		3·5	●	●	4·5	

FIG. 2.



HOUR.	PA FISS HT.	P SIZE	R.	L.	P SIZE.	PA. FISS. HT.
	MM.	MM.			MM	MM.
9·45	8.5	2·25	●	●	3·25	7·5.
coc 3% 10	10.	3·25	●	●	4·5	10.
10·15	9.	3·75	●	●	5.	9.
10·30	9.	3·25	●	●	3·5	9.
10·45	10.	3·5	●	●	4.	9·5
coc. 3% 11·0	11.	3·25	●	●	3·5	10.
11·15	10.	3.25	●	●	3·5	10·5
11·30	10.	4.	●	●	6·25	10·5
11·45	11.	3·25	●	●	6.	12·5.
12	10	3·5	●	●	6·5	10·5
12·15	9·5	3·75	●	●	7.	8·5
12·30	9	4·75	●	●	7·5	8·5

FIG. 3.

The general results show that the right palpebral fissure was slightly higher than the left at the commencement of the observations and reached its maximum of 11 mm. seventy-five minutes after the first drop of cocaine, whilst the left palpebral fissure reached its maximum of 12·5 mm. two hours after the first application, the fissures opening by 1·5 and 2·5 mm. respectively at the end of the first fifteen minutes. The right pupil was 2·25 mm. to start with and reached its maximum of 4·75 mm. nearly three hours after the first application of cocaine, whilst the left pupil, starting at 3·25 mm., reached its maximum of 7·5 mm. nearly three hours after the first drop. The increases in height of palpebral fissures and sizes of pupils are not steadily and evenly progressive, but the graphs of the pupil of this latter set of observations show much less disparity than those of the March observations. With regard to the palpebral fissure, the disparity between the two sets of measurements is rather less striking, as the accompanying diagrams show (figs. 2 and 3).

DISCUSSION.

The inability to swallow even water, persisting for three weeks, is the salient feature of the case, and unique in the literature of the twenty-three cases consulted, where the dysphagia is confined to solids, though Foix, Hillemand, and Schalit [6] report a peculiar case which could swallow solids but not fluids.

The absence of the pharyngeal or nausea reflex may be the normal condition in some people, and we certainly found variation in this respect in our colleagues. In some normal people, as Pitres and Testut [7] express it, you may "promener" the finger around the epiglottis without result. The two most valuable signs of glossopharyngeal paralysis, according to Vernet [8], are the *mouvement de rideau* and the ability to swallow fluids but not solids. In our case, owing to paralysis of the right superior constrictor, stimulation of the left pharyngeal wall produced a drawn curtain movement towards the healthy side. Pitres and Testut [9] devote some fifteen pages to the discussion of the glossopharyngeal nerve. They regard it as supplying the superior constrictor, but Elliot Smith [10] declares that it supplies merely one muscle directly from the nucleus ambiguus, and that is the stylopharyngeus, which, according to the laryngologists [11] is of trivial importance in deglutition. In the main, leading authorities are agreed that the muscles of the palate and larynx are supplied eventually by the accessory part of the eleventh nerve. Divergence of opinion [12] in all probability is due not to defective observation but to slight variation in the pathways selected by the numerous axons of similar function from a composite nucleus in reaching their peripheral destination. For example, the sensory nucleus solitarius is responsible for taste, and no more divergent pathways from the tongue could be imagined than the routes of the chorda tympani and glossopharyngeal nerves. While the extremes of the minute solitarius mass may entrain with precision their definite routes, the fate of the individual nuclei from the intermediate zone must swing precariously in the delicate embryological balance for one road or the other when both are functionally identical, and this must be equally true when the motor nucleus ambiguus sends out its components via the ninth or the tenth or the eleventh nerves. In fact, the spinal accessory is a comparatively late comer in the phylogeny of the cranial nerves, for it is absent in fishes and amphibians, and first appears in reptiles, merely as an accessory root of the vagus. In the following it is not only simpler to concern ourselves with the nuclei of origin rather than with the nerves but more in accordance with our argument.

The symptom-complex of our patient is due to occlusion of the posterior inferior cellebellar artery, which, according to Stopford's [5] researches, supplies the dorso-lateral part of the medulla oblongata, although Foix, Hillemand and Schalit [6] maintain that in the upper part of the medulla this area is supplied by the artery of the lateral fossa, a branch from the basilar. They do not allude to Stopford's work, which is based on a larger number of cases. The degree of arterial variation, however, must always awaken reluctance to a rigid assertion regarding the implication of a particular vessel.

Damage of the spinothalamic tract accounts for the loss of pain and temperature on the opposite side of the body. We may deduce from this case that the fibres from the lower limb occupy the lateral portion of the tract.

Horner's syndrome is due to the affected pupillary nucleus which is placed by Combes [13] between the spinothalamic tract and the nucleus ambiguus, but Karplus and Kreidl [14, 15, 16] more recently maintain that the centre is in the hypothalamus (a point probably supported by the recovery of the pupil in this case), though they admit its mediation through the bulb. This medullary lesion does not produce such a marked contraction of the pupil as is seen in lesions of the sympathetic in the neck.

The nucleus ambiguus, partly affected, supplies the striated muscles of the palate, pharynx and larynx through the ninth, tenth, and eleventh nerves. Sachartschenko [17] states that 86 per cent. of cases of this type exhibit the triad of German authors, that is paralysis of palate, pharynx and larynx due to implication of the entire nucleus, but dissociation may occur, as in this case, the palate and pharynx together, or the larynx alone, being paralysed. Ramsbottom and Stopford [18] explain this as due to the rostral part of the nucleus ambiguus supplying the larynx, while the caudal part supplies the palate and pharynx; but Foix, Hillemand and Schalit [6], who investigated their case very thoroughly by serial section, came to exactly the opposite conclusion. From the embryological aspect it is more acceptable to regard the rostral part as innervating the palate and pharynx and the caudal part the larynx,[1] though the steps of development do not always conform to reasoned anticipation. The sensory nucleus solitarius, slightly affected, subserves taste through the ninth and tenth nerves and the pars intermedia of Wrisberg.

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[1] Professor Stopford is in agreement with this criticism. (Private communication.)

The dorsal nucleus of the vagus escaped, but we believe that the spasm of the œsophageal entrance was due to irritation of this nucleus. Van Gehutchen and Molhant [19] say it supplies the striated muscle of the upper and middle parts of the œsophagus and the non-striated muscle of the intermediate and lower parts. This nucleus is considered also sensory by Elliot Smith [20], but Ranson [21] does not accord it mixed function.

Although the clinical diagnosis is certainly easy there remain difficulties of explanation, which were increased rather than diminished in the perusal of some thirty texts. Why could the patient not swallow fluids? According to Starling [22], in swallowing solids, elevation and dilatation of the pharynx is induced by the bolus initiating a sensori-motor reflex from the isthmus faucium, followed by constriction of the upper pharynx with dilatation of the lower in front of the advancing bolus, but in the deglutition of fluids a general dilatation secures their transmission almost at once to the stomach, hence the comparative immunity of the œsophagus in the swallowing of corrosive fluids. The hemiparetic pharynx may be unable to negotiate a rough bolus, but why should the healthy side not function enough to transmit at least a trickle of water? As a matter of fact, Spiller [23] argues that the subsequent ability of these patients to swallow solids is due to compensation by the healthy side. Mollison [24] states that complete unilateral paralysis of the tenth nerve has only a trifling interference with deglutition.

One possibility is that the dorsal vagal nucleus was impaired, with the result that the sympathetic exerted a tonic contraction. While this appears to solve the problem it is against the accepted teaching that stimulation of the vagus constricts the upper striated fibres of the œsophagus and dilates the lower non-striated fibres. Again the sympathetic influence is usually dilator. Such statements, however, are current among laryngologists. Brown Kelly [25] states that section of the vagi alone, without stimulation, gives dilatation of the œsophagus without relaxation of the cardia, which would be the final result if the innervation were purely vagal, but the supervening tonic contraction of the autonomous nervous system produces overaction or spasm. Kuntz [26] points out that section of the vagal fibres which supply the lower portion of the œsophagus and the cardia results in spastic contraction of these parts [36], the spasm subsiding after a few days, as the parts involved resume functional activity, which continues in an apparently normal manner. Brown Kelly further remarks that while dysphagia for solids is the principal symptom of œsophageal paralysis, the dysphagia is rarely purely œsophageal and that motor and sensory paralysis of the pharynx are vitally important as affecting the second phase of deglutition. Then again Munro Cameron [27], after insisting that the inferior constrictor is continuous with the longitudinal fibres of the œsophagus, the striated muscle of which has no Auerbach's plexus between its layers, and that the "ascending pharyngeal branch" from the superior cervical ganglion supplies the inferior constrictor, leaves us to conjecture how far this sympathetic supply may determine the onset of spasmodic contraction, and continues that if sensation from the mucous membrane is abolished then the muscle does not react normally, and contraction is evoked by the presence of food on the muscle, or through some unusual sympathetic stimulation, with the result that spasm of this sphincter or any sphincter develops. Now Kuntz [28] mentions that no antagonistic action between the vagus and sympathetic innervation of the œsophagus has been shown in any animal; Samson Wright [29] states that there are apparently no sympathetic fibres to the œsophagus; Gaskell [30] considers there is no evidence that motor sympathetic fibres reach the œsophagus and that its motor supply is entirely vagal. Again, Hofer and Spiegel [31], having removed all possible source of œsophageal sympathetic supply, could find no alteration in deglutition, while Inoaka [32, 33] could elicit no reaction by stimulation of the extrinsic sympathetic nerves of the œsophagus in the dog. It is true that there are illustrations depicting a profuse leash of sympathetic fibres streaming to the œsophagus, but as careful dissection has not enabled us to find even a few, it is possible that these diagrams may have been reproduced from one text to the other without verification.

At the moment we would be inclined to submit the following explanations in this case.

(1) The lesion has just been sufficient to cause irritation of the dorsal vagal nucleus, with resulting spasm of the œsophageal entrance. In opposition to this view is the clinical argument against such an intensive spasm persisting for three weeks. The clinician might be inclined to suspect an upper motor neurone lesion, and this would be possible on the same side of the medulla because the fibres after crossing do not immediately reach their nucleus. On the other hand, the spasticity associated with an upper neurone lesion would take a few days to develop, whereas the spasm in our patient was evident at the onset.

(2) In view of the fact that our patient thought he was swallowing

when the food was really behind his cricoid cartilage, probably the sensori-motor reflex from this area was interrupted so that no inhibition was placed upon the dorsal nucleus to cause its relaxation. In fact Ranson [34] describes secondary fibres running from the sensory nucleus solitarius to the nucleus ambiguus and also to the dorsal nucleus, in explanation of the reflexes.

To both these views there is still the argument that the healthy side ought to function for the swallowing of water, but against that is the fact that the vagus is segmental in its distribution to the œsophagus, not one vagus to one side even in the upper part. This forces the conclusion that the right side of this patient's medulla is responsible for the upper spastic segment of his œsophagus.

Textbooks are vague or evasive on the subject of swallowing. Barclay [35] is of the opinion that we do not swallow at all, but suck. He insists upon the variations which occur in normal people, a probable explanation of clinical discrepancies. In the interpretation of such a case there are many difficulties due to our ignorance of the extent of striated muscle supplied by the nucleus ambiguus and the areas wherein these muscles are represented in the nucleus, and due to the fact that our knowledge of deglutition is both elementary and speculative.

SUMMARY.

This article deals with a case of lateral syndrome of the medulla in a man of 62 years, exhibiting complete inability to swallow solids or fluids, Horner's syndrome of the right side, paralysis of the right side of the palate, defective sensation of taste on the right side of the tongue, abolition of the nausea reflex, *mouvement de rideau* of the pharyngeal wall, and defective sensibility to pain and temperature on the left lower extremity and trunk up to the umbilicus.

In the light of the conflicting views expressed in the literature, the anatomical, physiological, and clinical features of the case are presented with especial reference to the neurological mechanism of swallowing, and the condition of the pupils examined at the onset of the illness is contrasted with their subsequent examination, five months later, after partial recovery.

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A CONTRIBUTION TO THE CORTICAL REPRESENTATION OF VISION.

BY GORDON HOLMES.

THERE can be little doubt that the main lines of the cortical localization of visual perception in the area striata of the calcarine region of the occipital lobe as it is now generally accepted will ultimately prove correct. It is, for instance, definitely established that macular vision is represented near the pole of the hemisphere and the peripheral portions of the fields more anteriorly, while the upper quadrants of the retinæ correspond with the dorsal and the lower with the ventral parts of the areæ striatæ. It is generally accepted too that there is an accurate projection of the homonymous halves of the two retinæ on the opposite calcarine cortex.

Certain details of this localization still remain to be worked out. During the war of 1914-1918 I had the opportunity of examining several hundred men with gunshot wounds of the occipital lobes, and one striking observation which I made repeatedly during the early stages of such wounds was that, though the wound was apparently limited to one hemisphere, the blindness extended into the homonymous ipsilateral fields. In such cases the loss of vision almost invariably lay along the vertical axes through the fixation points, and generally became wider towards the upper or lower limits of the fields. I consequently called them "sector scotomata." This sector area of loss of vision might be found either above or below the fixation point, or both; it rarely extended to the upper or lower periphery. After observing a certain number of such cases it was found that such sector scotomata were generally caused by relatively large missiles of low velocity which had entered one occipital lobe obliquely or from the side and had been arrested by the falx separating the two occipital poles. I therefore concluded that the sector-like scotoma on the side of the wound was due to bruising or other damage of that portion of the calcarine area exposed on the mesial surface of the opposite hemisphere where this lies in contact with the falx.

This assumption was strengthened by a case in which a wound immediately to the right of the middle line, slightly above the posterior end of the calcarine fissure, produced, in addition to left homonymous paracentral scotomata, right-sided sector scotomata extending from the fixation points downwards between the vertical meridians and the radii 20° from them; it was found that two fragments of the skull had been driven through the falx immediately above the level of the posterior calcarine fissure in such a position that they probably injured only the upper superficial part of the left area striata.

From these and other observations I concluded that those portions of the retinæ which lie along the vertical meridians are represented on the exposed mesial surfaces of the occipital lobes, and, by exclusion, that the retinæ along the horizontal meridians are projected on to that part of the area striata which lies in the walls of the calcarine fissures [3, 4].

Later I discovered that Henschen [1, 2] had already suggested this further functional subdivision of the visual cortex. In a case in which Wilbrand had found by perimetric examination narrow homonymous scotomata extending from the fixation points along the horizontal radii to about 60°, Henschen demonstrated a small softening in the floor of the opposite calcarine fissure, and therefore concluded that the horizontal segments of the visual fields are represented in the bottom of the calcarine fissures.

The following case tends to confirm this conclusion:—

B. J., a married woman, aged 32, was admitted to the National Hospital on February 11, 1931, complaining of headache and disturbance of sight.

She came of a healthy family and her previous health had been good. Her first pregnancy terminated in a stillbirth, the second by Cæsarean section three and a half years previously.

For six months before admission she had suffered with headaches, chiefly on waking, and when the pain was severe she was conscious of a blowing sound in her head, mainly to the right side. In the middle of December, 1930, after an attack of influenza, the headaches became more intense in the temporal and occipital regions. A month later, during an attack of severe headache and vomiting, golden figures of simple types, as crosses, X's, and Z's, suddenly appeared in front of her eyes and her sight became dim. She was unable to remember if these figures and the dimness of vision were limited to any portion of the visual fields. This attack lasted about one hour but recurred next morning for a shorter time. Vision became normal quickly after each attack. Her headaches grew gradually more intense and were aggravated by sneezing, coughing or stooping.

On January 29, after a severer bout of headache her vision became again affected and, according to her own story, she lost consciousness for the next week. Her husband stated, however, that during this time she complained of pain, replied to questions and took food, but lay immobile. Since this attack her sight has been affected, but it has improved a little; on attempting to read she has been unable to see words to the left of that at which she looked. Her limbs and speech have been unaffected, and she has not been subject to fits or convulsions. Her general health has remained good. Her cerebro-spinal fluid, obtained a few days after the attack of January 29, by her family doctor, was slightly blood-stained.

On examination she was a well nourished healthy looking woman. Her heart and blood-vessels were normal, and her blood-pressure within natural limits. There was a small port-wine-coloured nævus on her right cheek, lateral to the external angle of the orbit. She was bright and intelligent, and all her mental functions seemed to be normal.

Her ocular movements were unrestricted, but a slow coarse horizontal nystagmus developed on deviation to either side, consisting of slow recessions to the mid-line and quicker return jerks in the direction of voluntary deviation. The rate of the jerks was slower to the right. The left pupil was larger than the right, but both reacted to light and on convergence. The lower part of the left side of her face moved less briskly than the right on voluntary effort, but the functions of the other cranial nerves were normal. There was no disturbance of hearing.

The size and tone of her muscles were unaffected, but when unsupported her left arm did not maintain its posture as well as the right, and the left grasp was slightly weaker than the right. There was no disturbance of co-ordination. In walking she tended to deviate to the left and her left arm did not swing. Sensation was undisturbed. The left tendon-jerks were brisker than the right, but the abdominal reflexes were equal and the plantar reflexes were of the normal flexor type.

A month later she was slower in recognizing the shape of objects placed in her left hand than in her right, and on testing tactile discrimination with compass points she made mistakes on the left palm when the points were separated from one another to a distance at which she made no errors on the right palm.

She stated that on three occasions, at intervals of about half an hour on the one day, after someone had walked past the foot of her bed from left to right, she had for a moment or two the impression of the same person as before walking past, but when she looked carefully the person was not there. The dress, size and distance of the person appeared exactly the same, but the image was more shadowy.

Her visual acuity uncorrected was right $\frac{6}{12}$, left $\frac{6}{18}$. Her retinæ were normal, but the upper nasal quadrants of her discs were blurred, and later the upper edge of the right disc became œdematous. Her visual fields were repeatedly mapped out by different observers (fig. 1) and on each occasion a partial left homonymous hemianopia was found, the striking feature of which was that though the blindness came up to the fixation points along the horizontal meridians, there was a considerable escape along the vertical meridians in the upper and lower quadrants. In the last fields which were charted (fig. 2), two days before her death, the blindness still reached the fixation point, but some recovery of vision was found, especially in the lower quadrants. The degree of hemianopia varied, probably under different functional conditions, as on one occasion (March 5) there was less escape in the upper and lower quadrants.

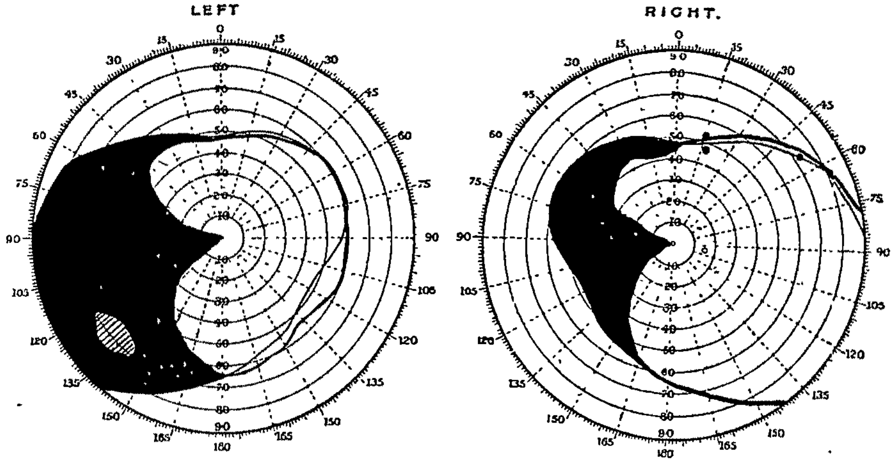

FIG. 1.—Visual fields recorded on February 20, 1931, with a white object one degree in diameter.

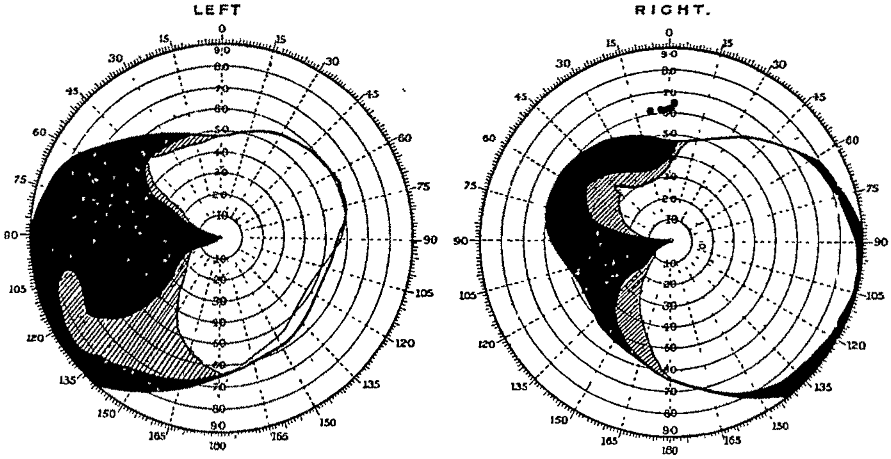

FIG. 2.—Visual fields on March 11, to a white object one degree in diameter. In the blackened area vision was completely lost, in the shaded areas moving objects were perceived.

Radiograms of the skull revealed no disease. On admission her cerebrospinal fluid was clear and colourless, but it contained 15 small mononuclear cells per centimetre and the total protein amounted to 0·06 per cent. The Wassermann was negative in both the fluid and blood.

The diagnosis was made of a cerebral tumour in the right occipital lobe, probably involving the floor of the calcarine fissure.

On March 13, Sir Percy Sargent operated, opening the skull by a large osteoplastic flap over the right parieto-occipital region. The dura was under great tension, and before it was incised 20 c.c. of hypertonic saline was given intravenously to reduce pressure. On exposing the brain two enormously dilated vessels were found on the surface of the hemisphere, the most anterior being probably the Sylvian vein. They were connected by numerous anastomosing channels. A densely packed mass of vessels was also found on the lateral aspect of the occipital lobe. Owing to the severe degree of pressure and the patient's condition it was decided to make no attempt to deal with the condition at this operation. She died without apparent cause the same evening, forty-four days after the onset of the hemianopia.

Autopsy.—There was very little hæmorrhage at the site of operation. After removal of the brain a carmine gelatine preparation was injected under pressure into the right carotid artery after tying off the anterior communicating artery. The veins were also injected by a blue gelatine preparation.

On examining the brain several large vessels, some arteries, some veins, were seen to issue from the middle of the right Sylvian fissure. One large vein ran across the postcentral gyrus to the superior longitudinal sinus, another over the temporal lobe to the superior petrosal sinus. Other large veins connected with the lateral sinus and the posterior part of the longitudinal sinus. The arteries passed mainly backwards to a tangled, tightly packed mass of vessels, mainly injected red, on the lateral aspect of the occipital lobe in the position of the anterior occipital sulcus. The veins from this hæmangeioma drained into the longitudinal and lateral sinuses. The mesial surface of the hemisphere appeared normal.

After hardening in saline formaline the brain was divided by a series of coronal sections. In these it was seen that though the angeioma lay mainly on the surface of the brain many abnormally large vessels with thin poorly developed walls were present in the neighbouring and underlying sulci and a few penetrated into the white matter beneath the tumour. The cortex beneath and around the angeioma was damaged, probably at the operation or by the post-operative bulging of the brain into the trephine opening.

In addition a large hæmorrhage was found extending longitudinally through the occipital lobe, from the level of the hippocampus up to the tip of the pole. It was enclosed in an organized ochre-coloured capsule and in the hardened specimen seemed to be shrinking away from the capsule and the surrounding brain tissue, which seemed almost intact. It was evidently of considerable age, and its histological as well as its naked-eye appearance leave little doubt that its occurrence was responsible for the symptoms which appeared six weeks before death.

At its anterior end it lay lateral to and slightly below the wall of the posterior horn, but a little further posteriorly it broke into the ventricle and extended backwards in this position almost to the tip of the horn, to which it again lay lateral; behind the ventricle it occupied the white matter of the occipital lobe, directly opposite the bottom of the calcarine fissure.

The occipital lobe was cut in serial sections; every fifth was stained by the Weigert-Pal method and many intervening ones with carmine in order to study the structure of the tissues around the hæmorrhage. The most striking features of these sections was the clearly cut border of the lesion; the Weigert-Pal sections revealed very little injury of the fibres immediately around the hæmorrhage, and the changes visible in carmine preparations were slight. Within the hæmorrhage no nervous structures were visible.

One centimetre from the occipital pole of the hemisphere the hæmorrhage, which in its vertical diameter measured about 5 mm., lay in the white matter immediately lateral to the floor of the calcarine fissure, which was here represented by a shallow groove; all the tissues to within less than 1 mm. of the cortex were destroyed and the subcortical fibres rarefied (fig. 3). No changes were detected in the cortex. The upper and lower portions of the striate area and the white matter under them were unaffected. At this level the lesion extended lateral-wards to the cortex but did not involve it.

The hæmorrhage continued to occupy the same position in relation to the calcarine fissure as it was traced forwards to the annectant posterior cuneo-lingual gyrus where more subcortical white matter remained, but it was considerably rarefied (fig. 4). In front of this the lesion extended more dorsally, but the medullated fibres on the upper and lower walls of the fissure were well preserved and cortex was normal.

Where the ependymal cells of the posterior horn of the ventricle first appeared the coronal sections included the main mass of the angeioma. Here the hæmorrhage extended as a narrow horizontal slit, between $\frac{1}{2}$ and $\frac{2}{3}$ cm. in breadth, to the lateral aspect of the hemisphere, reaching but not involving the cortex. Its medial end came up to the non-patent tip of the horn and involved part of the sagittal strata here; there was also a small area of degeneration along the mesial border of the ventricle, immediately opposite the calcarine fissure. The fibres on the ventral margin of the horn were, however, not affected and stained normally.

From the opening of the posterior horn almost to the level of the hippocampus the lesion had broken into the ventricle, so that only its ventral part was recognizable in the sections. Most of the white matter on the floor of the calcarine fissure had disappeared or was represented by a few poorly stained fibres only, but in many places the cortex had escaped and presented surprisingly little histological change apart from a rarefaction of its radial fibres immediately above the lesion. The fibres of the sagittal strata around the ventral margin of the horn were preserved and stained well; the dorsal margin of these strata also escaped direct damage, though the fibres of the internal stratum at least did not stain as darkly as normally. The cortex along the walls of the calcarine fissure and that on the mesial surface of the hemisphere and the subjacent white matter were intact (fig. 5).

Towards the anterior end of the calcarine fissure, where the area striata is limited to its lower wall, the bottom of the sulcus was denuded of white matter and the middle portions of the sagittal strata were entirely destroyed, but the

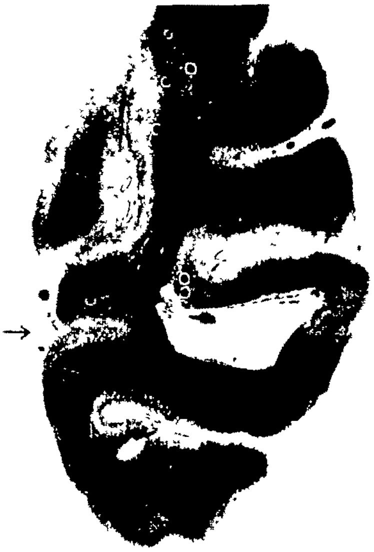

FIG. 3.

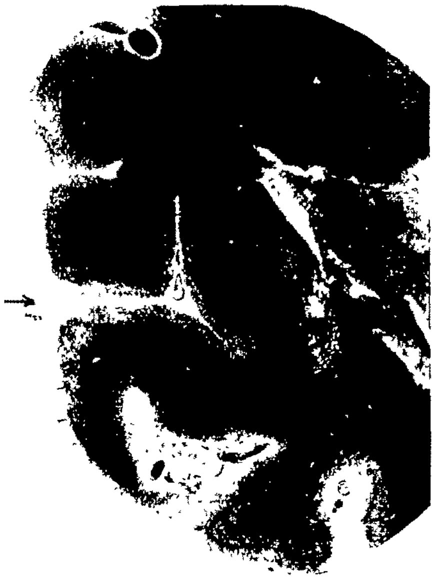

FIG. 4.

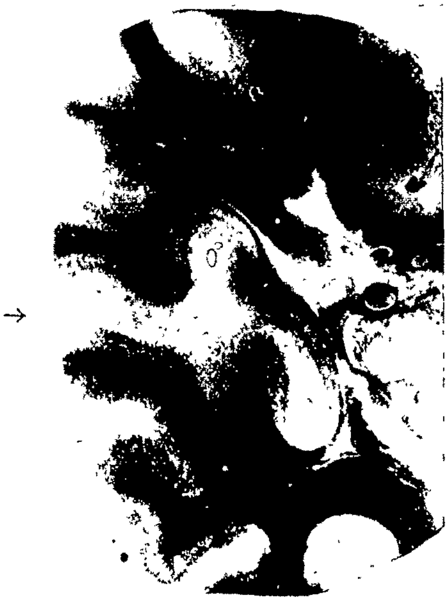

FIG. 5.

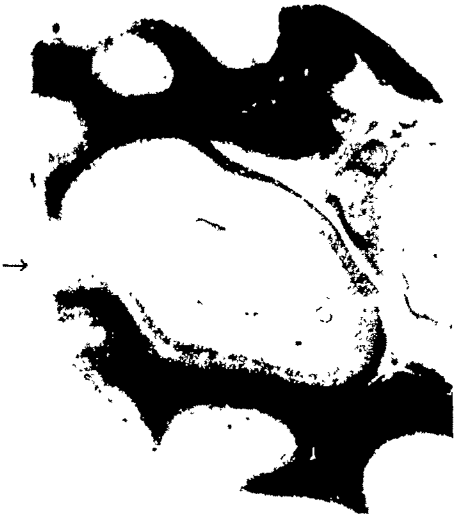

FIG. 6.

FIGS. 3-6.—Photographs of sections through the right occipital lobe stained by the Weigert-Pal method. In each photograph the calcarine fissure is indicated by an arrow.

dorsal and ventral margins of the strata were well preserved and fibres from them could be followed mesialwards into the white matter on the mesial aspect of the hemisphere (fig. 6).

Anterior to this level the lesion diminished in size, lay lateral to but involved the middle portion of the lateral wall of the posterior horn and extended through the middle part of the sagittal strata, but it left intact considerable portions of their dorsal and ventral margins.

One fact brought out by the histological examination of this case is the destruction of the middle portions of the sagittal strata of the occipital lobe by the hæmorrhage and the intactness of their dorsal and ventral fibres. In the Weigert-Pal preparations these stained quite well, and as the patient lived for forty-four days after the onset of the lesion sufficient time had elapsed for degeneration to have appeared in them if they had been interrupted in any part of their course. It is now generally agreed that the geniculo-calcarine fibres run mainly at least in the external stratum, that is the so-called inferior longitudinal bundle, rather than in Gratiolet's optic radiations, and it was in it that most fibres were preserved.

Further, the subcortical white matter along the floor of the calcarine fissure was involved along the whole length of the fissure to such a degree that few afferent fibres could have reached the cortex, and in places the cortex itself had suffered.

On the other hand the cortex and the subcortical white matter on the mesial surface of the brain and along the lips and the adjoining portions of the walls of the calcarine fissure had escaped injury and presented no evidence of disease or degeneration. Further, fibres could be traced from the dorsal and ventral borders of the sagittal strata into the white matter of these portions of the cortex.

From the site of the lesion and the structures involved by it, it seems justifiable to conclude that no afferent impulses could have reached those portions of the striate cortex buried deeply in the calcarine fissure and that therefore vision subserved by these parts of the cortex was lost, while the cortex on the mesial surface of the brain and along the lips of the calcarine fissure being intact and receiving afferent geniculo-cortical fibres was capable of function.

On correlating the anatomical lesions with the changes present in the visual fields it becomes probable that the sectors on each side of the horizontal meridians are represented in the cortex buried within the calcarine fissure, while the sectors adjacent to the vertical radii correspond with the striate cortex exposed on the surface of the hemisphere and along the lips of the fissure. The greater loss in the peripheral portions of the homonymous fields, and the narrower area of blindness in the regions of the fixation points, would correspond with the larger proportion of the area striata affected or deprived of afferent fibres in the anterior calcarine region and the relatively smaller extent of the lesion towards the pole of the hemisphere (compare figs. 3 and 6).

This localization could be conclusively demonstrated only if the cortex alone was damaged, as it was in Henschen and Wilbrand's case, though here the lesion was too small to permit a general conclusion. In my case the middle portions of the sagittal strata containing the optic radiations were destroyed in a considerable portion of their extent. It is therefore necessary to assume that the dorsal and ventral fibres of the radiations carry impulses from the corresponding quadrants of the retinæ and pass to the upper and lower margins of the area striata. Henschen and others have postulated this anatomical arrangement, but unaware of his work owing to literature not being available to me during the war, I put forward the same conclusion from observations on gunshot wounds of the occipital lobes, and suggested that in the radiations the fibres are arranged regularly in laminæ according to the origin of the impulses they carry, and that those indirectly connected with the upper and lower quadrants of the retinæ are probably contained in distinct bundles separated by an anatomical interval [3]. Rönne [5] has come to the same conclusion. If this assumption is correct it would appear that impulses from the corresponding parts of the two retinæ are carried mainly in the fibres, uninjured in my case, on the upper and lower margins of the sagittal strata. Some of these fibres pass normally to the cortex in the depth of the calcarine fissure, but these must have been interrupted in the subcortical white matter by the lesion which involved this. The fibres to the upper and lower margins of the area striata were unaffected by this lesion and consequently able to reach the cortex on the surface of the brain and along the lips of the calcarine fissure.

It is probable that that portion of the lesion adjacent to the bottom of the calcarine fissure was the chief factor in determining the changes in the visual fields present in my patient, and the case is therefore further evidence that the sectors of the retinæ along their horizontal axes are represented in the cortex around the floor of the calcarine fissure.

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REFLEX-GRASPING ASSOCIATED WITH TUMOURS NOT INVOLVING THE FRONTAL LOBES.[1]

BY PAUL C. BUCY.

IN neurology we are not infrequently confronted with a new sign or symptom which is advanced by its recorders as indicative of a certain pathological lesion. When the constancy of such signs can be adequately confirmed by numerous well-studied cases they become valuable aids to diagnosis; but when they are inadequately established they may be sources of error, especially in the localization of tumours, until their full significance is revealed.

In the past few years, reflex-grasping (" forced grasping "; " Zwangsgreifen," &c.) has received much consideration (Schuster [8 and 9], Schuster and Pineas [10], Schuster and Casper [11], Adie and Critchley [1], Freeman and Crosby [3], Janischewsky [5], &c.). It had previously been the subject of discussion by Janischewsky [4], Wilson and Walshe [12], and others. As a result, reflex-grasping has become associated by many clinicians exclusively with lesions of the frontal lobes. Adie and Critchley have gone so far as to say " that their presence (forced grasping and groping) in a patient with cerebral tumour is unequivocal evidence of the situation of the tumour (frontal lobe)."

Other authors have realized that such an extreme statement is not warranted. Janischewsky [5] states, "Die Bedeutung des Greifreflexes als fokales Symptom wird vermindert in den Fällen in denen ein Hydrocephalus internus vorhanden ist." Fedorovoa [2] has expressed a similar opinion, while Freeman and Crosby, speaking of the reflex in unconscious patients with generalized cerebral disease (not tumour), state, " It is bilateral and it does not have any especial localizing value."

I wish to describe two cases of tumour of the brain, one a tumour of the fourth ventricle with a marked internal hydrocephalus and the other a large neoplasm in the right occipital lobe, in both of which *bilateral reflex-grasping* was present.

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[1] From the Division of Neurology and Neurosurgery, University of Chicago.

Case 1.—*Convulsions, weakness, vomiting, headache, blurring of vision; stuporous and catatonic. Bilateral reflex-grasping, perseveration of movement, varied pyramidal signs. Ventriculography revealed right occipital tumour. Partial extirpation of a glioblastoma multiforme. Death six months later.*

L. S., a male, aged 48, a Jewish shoe repairman, was referred to this clinic by Drs. Andrew Rosenberger and S. M. Turkeltaub of Milwaukee, Wisconsin. He was admitted on February 16, 1930, complaining of weakness and convulsions since September, 1929.

In September, 1929, while at work the patient was suddenly seized with a convulsion. He was told that he frothed at the mouth and "shook all over." He became unconscious and was taken to a hospital where he awoke several hours later with a cutaneous wound in the left temporal region. He returned to work the next day, although he complained of general weakness for several days. On the morning of October 27 at 2 a.m., the patient arose from his bed, vomited, cried out, and suddenly lost consciousness. In the course of a few minutes he had five or six generalized convulsive seizures, following which he was stuporous for the next twenty-four hours. During this time he was unable to say more than a few words because his tongue seemed thick and swollen; within four or five days his speech became normal. Three days after these nocturnal convulsions he returned to work, although he remained weak for several days.

On November 11, 1929, he was admitted to another clinic where examination revealed a depressed man, weighing 109 lbs. (he had lost 13 lbs. in the preceding eight weeks), with a blood-pressure of 115/84, and a pulse of 70. His vision was $\frac{6}{6}$ in the right eye and $\frac{6}{15}$ in the left. His visual fields on rough testing were not defective. There were no other abnormal findings. X-ray of the skull, examination of his urine and the Wassermann test on the blood revealed nothing abnormal.

He was discharged from the first clinic, in which the possibility of a brain tumour had been realized, on November 20, and was requested to return in a few months, but did not do so. Subsequently he had no more convulsions but became progressively weaker and gave up work about February 1, 1930.

Two weeks prior to admission to the Billings' Memorial Hospital of the University of Chicago, he had an attack of projectile vomiting, the first since the series of convulsions in October. On the morning of admission he vomited again. For about a month prior to admission he had suffered from headache over his eyes. For two months he had complained of blurring of his vision.

Past history: Seven years prior to the onset of the present illness the patient had fallen 25 ft. from a ladder, injuring his right shoulder. Ever since that time he has complained of pain in that shoulder and weakness of the right upper extremity.

These facts were elicited from the patient's relatives and the records of the other clinic, as he was too stuporous and un-cooperative to give a satisfactory story.

Examination (February 17, 1930): The left pupil was slightly larger than the right; both were round and reacted sluggishly to light and more markedly so to accommodation. On ophthalmological examination of the fundi, marked blurring of the disc margins and a papillœdema of the two dioptres were seen. There were numerous hæmorrhages about the discs. It was impossible to determine the visual fields because of lack of co-operation.

A slight bilateral weakness of the external recti was present. There was a slight paresis of the left side of the face in voluntary movements; a definite weakness of the flexors of the head on the neck, with apparent atrophy of the anterior neck-muscles; some weakness of the extensors of the right forearm as compared to the left; a marked weakness of both deltoids; definite lateral displacement of the right scapula on extension of the arms, with atrophy of the muscles of the right shoulder-girdle. There was a tendency toward catatonia, the upper extremities remaining for considerable periods of time in any position in which they were placed. There was also a moderate increase in muscular rigidity which was of a plastic type, not unlike the "lead-pipe rigidity" of catatonic states.

There was a definite and obvious reflex-grasping in both hands. Whenever an object was drawn across the palms of the patient's hands the fingers closed upon it and grasped it firmly. Efforts to withdraw the object caused the force of the grasping to increase. The patient also experienced great difficulty in relaxing either the reflex-grasping or voluntary grasping.

There was also marked perseveration of movement, i.e., after a given movement was performed the patient persisted in repeating this movement several times. Strength was good in both lower extremities and no abnormality of movement was detected. The deep reflexes in the upper extremities were diminished but equal. The abdominal reflexes were active and equal. The patellar tendon reflexes were active and equal on the two sides, while the right Achilles-tendon reflex was more active than the left. The plantar reflexes were normal. The patient walked with short slow steps and occasionally tended to sway backward.

On February 18 conjugate movement of the eyes to the right was defective and there was a tendency to jerk back to the mid-line. The left wrist-jerk was brisker than the right and the left patellar tendon reflex was more active than the right. On this date the patient's slowness in comprehension was even more marked. He had difficulty in retaining ideas, in executing commands and on one occasion was unable to find his bed.

Because of the resemblance of this patient's condition to the catatonic states and because of the reflex-grasping it was thought that probably he was suffering from a tumour of one of the frontal lobes. However, as the lateralizing signs had not been consistent and because of the previous injury to the right upper extremity which made proper evaluation of signs in the upper extremities impossible, it was decided to resort to ventriculography in order to determine which frontal lobe was involved.

Ventriculography: On February 20, 1930, under novocain-anæsthesia, an incision and trephine opening were made in the right occipital region. A needle was then inserted into the cerebral tissue and at a depth of 3 cm. entered a cystic cavity from which 5 to 6 c.c. of yellow fluid, which coagulated on standing, were obtained. It was obvious, therefore, that we had punctured a gliomatous cyst. The cystic cavity was filled with air and the wound closed. A similar opening was then made in the left occipital region. Clear colourless fluid was obtained from the left lateral ventricle and a small quantity (10 c.c.) of air injected. X-rays of the skull following this procedure revealed a small cystic space 2 to 3 cm. anterior to the occipital portion of the skull and 3 or 4 cm. above the level of the tentorium cerebelli.

Following the puncture of the cyst and the ventricle the patient was considerably brighter. Unfortunately the presence or absence of reflex-grasping was not recorded.

Operation: On March 1, 1931, an osteoplastic flap was reflected in the right parieto-occipital region. The cyst was again punctured and 10 c.c. of yellowish fluid were obtained. On reflecting the dura a greyish neoplasm was seen on the surface of the occipital lobe, about 4 cm. in diameter. As much as possible of the tumour was removed with the electric cautery, but as it was large and infiltrated the surrounding brain tissue, it was impossible to remove all of it. A decompression was made over the tumour and the wound closed.

Microscopical description (N-30-22): The tissue removed at operation was cellular. The nuclei varied greatly in size and shape and there were numerous mitotic figures. There was a goodly number of unipolar and bipolar spongioblasts present. Many multinucleated giant cells were seen scattered throughout the tissue. Cajal's gold-sublimate method revealed many spongioblasts, astroblasts and astrocytes. In some areas there was considerable extravasation of blood into the neoplasm and numerous small necrotic areas were seen. Intervascular necrosis, forming pseudo-palisades, was common. Throughout the neoplasm blood-vessels were very numerous. In some parts of their walls both the endothelium and the connective tissue showed considerable proliferation, which was well shown in preparation impregnated by Perdrau's method.

This tumour was a typical glioblastoma multiforme.

Course: Following the operation the patient had a rather stormy course partially due to the breaking down of the wound which drained for a long time following the operation. On one occasion a rubber tube which was being inserted into the cavity of the tumour was pushed into the lateral ventricle, resulting in a drainage of cerebrospinal fluid for two or three days.

He gradually recovered his general strength although he had a mild left hemiplegia. *Reflex-grasping was never elicited after the operation.*

On April 23, the visual fields showed a complete left homonymous hemianopsia with sparing of macular vision. Ophthalmoscopic examination revealed a mild secondary optic atrophy on the right.

The patient was given a course of Roentgen-therapy and discharged on May 11, much improved except for a small mass at the site of the decompression.

He was readmitted on May 28, because of continued growth of the mass and slight breaking down of the wound. The mass continued to grow rapidly and he gradually developed a complete left hemiplegia. His general condition gradually became worse and he died on August 30, 1931.

Necropsy: A necropsy was performed fifty minutes after death. The findings, other than those in the nervous system, were moderate emaciation; acute hypostatic hyperæmia, œdema and broncho-pneumonia of both lungs; acute purulent bronchitis; brown atrophy of the myocardium and liver; atrophy of the spleen; moderate generalized arteriosclerosis; bilateral fibrous and calcified apical tuberculosis of both lungs.

Gross description of the cranium and its contents.—As the scalp was removed the tumour was found underneath it extending to the right mastoid, to the forehead and past the mid-line over the vault of the skull. The extracranial portion of the neoplasm was vascular and contained many small hæmorrhages. It measured 11 cm. above the surface of the skull and is 9·5 by 12 cm. in cross section. This was surrounded by a tough, white, avascular cartilaginous-like tissue. At the point of connection of the extracranial with the intracranial portion, the tumour was softer and contained areas of necrosis.

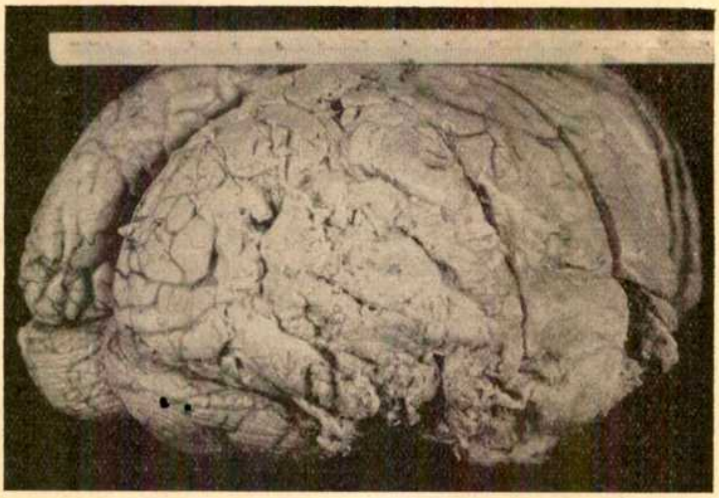

FIG. 1 (*Case* 1).—Glioblastoma multiforme occupying the right occipital lobe and extending forward into the temporal lobe. It also involves a small portion of the postero-inferior part of the parietal lobe.

The intracranial portion of the tumour occupied the antero-inferior part of the right occipital lobe, the posterior portion of the temporal lobe and a small part of the postero-inferior area of the parietal lobe (fig. 1). The right hemisphere was larger than the left and there was a displacement of the median longitudinal fissure and the ventricular system to the left. There was no tumour in the anterior end of the temporal lobe, the anterior or superior portion of the parietal lobe or in the frontal lobes. Sagittal sections revealed the

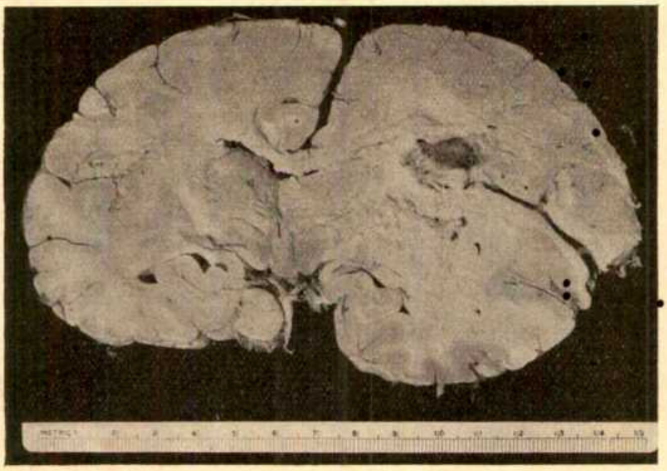

FIG. 2 (*Case* 1).—Anterior end of tumour lying lateral to the right thalamus in the region of the internal capsule. There is also a round mass of tumour lying in the Sylvian fissure. It is the same colour as the neighbouring cerebral tissue. This section is on a level with the anterior limit of the pons, a small portion of which is visible in this photograph.

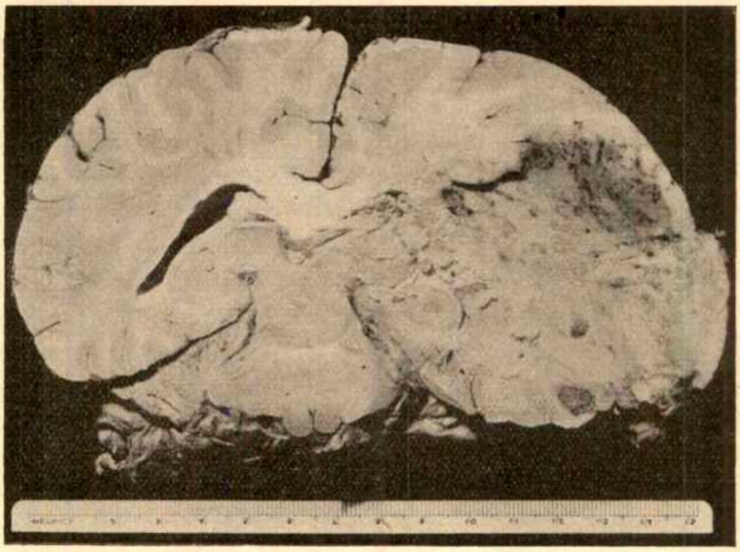

FIG. 3 (*Case* 1).—Coronal section through the centre of the neoplasm. There are numerous areas of hæmorrhage and necrosis.

anterior end of the tumour on a level with the anterior end of the pons. At this point it involved the internal capsule and extended medially to the lateral margin of the thalamus (fig. 2). It extended backward and downward from this point into the occipital and temporal lobes. The tumour was not encapsulated, was vascular and contained areas of hæmorrhage and necrosis (fig. 3). The lining of the lateral ventricles was ragged throughout.

Microscopical description.—The intracranial portion differed from the tissue removed at operation only in that there were numerous large areas of necrosis and hæmorrhage and an extensive ingrowth of connective tissue into some parts of the tumour.

The extracranial portion was composed of a dense connective tissue framework which enclosed small islands of tumour tissue similar to that within the brain. There were also many very large areas of necrosis.

The ventricular wall showed an absence of the ependyma, except in a few small areas, and a necrosis of some of the subependymal tissue.

DISCUSSION.

It must be remembered that reflex-grasping was only observed in this patient in February 1931, prior to the operation. At this time the tumour seemed limited to the occipital lobe and posterior part of the parietal lobe. That portion of the tumour which at necropsy was seen to extend forward into the region of the internal capsule, the thalamus, and the occipito-frontal bundle is undoubtedly a late development which occurred during the six months that intervened between the operation and the patient's death. This is indicated by the absence of a hemiplegia prior to the operation. In any event a lesion in one hemisphere in this situation cannot be regarded as responsible for all reflex-grasping. Whatever the correct explanation of the presence of reflex-grasping may be in this case, it is obvious that it is associated with intracranial tension. There is no other apparent explanation for the fact that the phenomenon was present before operation and disappeared after a partial extirpation of the glioma had been done and a decompression made. Certainly the pathways involved in the production of the reflex-grasping could not have been destroyed by the neoplasm; more probably only a physiological block, which was removed with the relief of tension, was present.

The raggedness of the ventricular walls is in all probability secondary to the accidental puncture of the right lateral ventricle through an infected cavity and a resultant mild inflammatory process. It is also to be noted that at no time did this patient have a marked hydrocephalus.

Case 2.[1]—*Headache, vomiting, choked disc, paralysis of vertical conjugate movement of the eyes. Bilateral reflex-grasping. No operation. Death. Necropsy. Ependymoma of the fourth ventricle.*

This patient, a young girl between the ages of 15 and 20, was seen in the clinic of Professor O. Foerster, of Breslau, Germany. She presented the signs and symptoms of a markedly increased intracranial tension (headache, vomiting, choked disc, &c.). Clinically very few focal signs could be elicited except for a paralysis of upward movement of the eyes and a marked bilateral reflex-grasping—whenever her hand caught on the bedclothing, or when an object (such as the handle of a reflex-hammer or the examiner's fingers) was drawn across her palms, the fingers would immediately close firmly on the object and any effort to withdraw the object would cause the grasp to tighten.

The patient's condition rapidly became worse and she died before an operation could be performed. Necropsy revealed a severe internal hydrocephalus including a marked dilatation of the fourth ventricle upward. The ventricular system was obstructed by a relatively small tumour which proved to be an ependymoma in the posterior portion of the fourth ventricle. Except for the hydrocephalus there was no involvement of the cerebral hemispheres.

DISCUSSION.

Janischewsky [5] has reported a case (No. 6) of cysticercosis of the brain, particularly of the base and of the brain-stem, with marked internal hydrocephalus, which presented bilateral reflex-grasping. Fedorowa has reported one case (Case No. 5) in which a glioma of the right parietal lobe produced a complete left hemiplegia and marked reflex-grasping of the right hand. In another case (Case No. 6) reported by the same author, the patient presented the signs of increased intracranial tension and reflex-grasping of the right hand. A diagnosis of a tumour of the left frontal region was made, and it was decided to perform an operation. Just prior to the operation a weak reflex-grasping developed on the left side. The operation was performed, revealing a marked increased intracranial tension, but no tumour. At the time of the report the site of the tumour had not been determined. It is true that reflex-grasping has occurred in several cases of cerebral arteriosclerosis with dilatation of the lateral ventricles and atrophy of the frontal lobes (Freeman and Crosby, Cases 3 and 4; Schuster and Casper, Cases 16 and 17; Kleist [6] Case 10), but as the pathological lesion was one of atrophy rather than of internal hydrocephalus from obstruction of the pathway of the cerebro-spinal fluid with resultant increased intra-ventricular tension, they do not seem to belong in this group. There was also evidence of atrophy of the frontal lobes in these cases of cerebral arteriosclerosis, while in the two cases reported here and in Janischewsky's case, No. 6, there was no evidence of any abnormality in the frontal lobes.

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[1] Professor Otfrid Foerster, of Breslau, Germany, has very kindly permitted me to mention this case here. Because of other interesting findings he proposes to report it in more detail at a later date.

Several hypotheses have been advanced in explanation of reflex-grasping. It is not my purpose here to discuss all of these hypotheses or to offer one of my own. The hypothesis and schema of Schuster and Casper seem to be the most applicable to the largest number of cases, and possibly these cases may be interpreted in the light of their work.

Many authors have dwelt on the relationship of pathological reflex-grasping to the reflex-grasping seen in infancy. It is reasonable to suppose that the disappearance of reflex-grasping in the infant is due to the development and myelination of a transcortical inhibitory pathway to the pre-Rolandic motor area which suppresses reflex-grasping in the normal human subject after infancy, and that the development of pathological reflex-grasping results from interruption of this inhibitory pathway, or, as Schuster and Casper expressed it, deinhibition ("Enthemmung"). On this basis they have postulated the existence of a hypothetical inhibitory tract, which agrees with the known course of transcortical fibre tracts within the cerebral hemispheres and can be correlated with their pathological studies.

The hypothetical inhibitory pathway is bilateral in its origin, i.e., the inhibitory innervation of each central area arises in both frontal lobes. This inhibitory pathway arises from the medial surface of the superior frontal convolution and of the gyrus cinguli, and passes downward to the region of the occipito-frontal fasciculus which lies just beneath the corpus callosum, lateral to the lateral ventricle, and above the caudate nucleus, and inferiorly rests upon the internal capsule from which it is not sharply demarcated. These fibres then pass backward to the level of the central area where some pass directly to the pre-Rolandic area of the homolateral hemisphere, while others cross in the corpus callosum to terminate in the central area of the opposite side. The course of this pathway will be most clearly shown by the accompanying illustration from the work of Schuster and Casper (fig. 4).

It is extremely questionable whether the two cases reported here, Janischewsky's Case No. 6, and Fedorovoa's Case No. 5, can be brought into accord with the hypothesis of Schuster and Casper. It is, of course, possible that the extreme degree of internal hydrocephalus in our Case 2 and the case of Janischewsky caused compression by the superolateral angle of the lateral ventricles in the region of the occipito-frontal fasiculus and thus of the "inhibitory pathway." Further, we might include Case 1 and Fedorovoa's Case No. 5 in which there was only a very mild dilatation of the ventricles (figs. 2 and 3) but a markedly increased intracranial tension, in such a hypothetical explanation. This appears to be a most fanciful explanation. However, as I have previously stated, it is not my purpose to furnish an explanation for this phenomenon, but I wish rather to stress the fact already established by Janischewsky and Fedorovoa that *in the presence of a marked internal hydrocephalus with increased intracranial pressure, the value of reflex-grasping as a localizing sign is greatly reduced.*

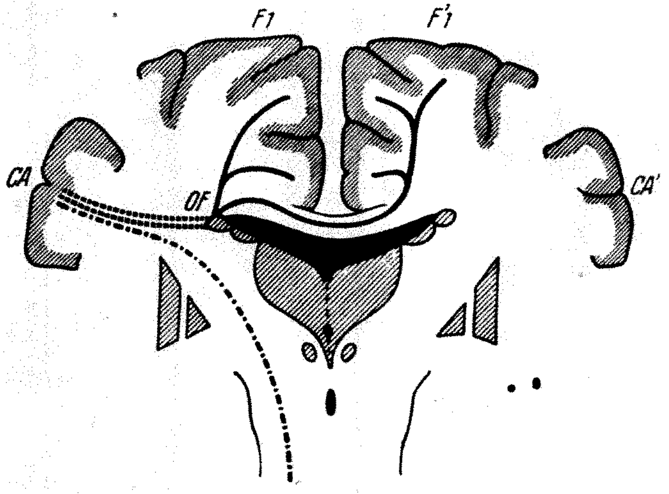

FIG. 4.—Schema of the "reflex-grasping inhibitory pathways." ——— and - - - - the inhibitory pathway from the medial surface of the superior frontal convolutions (F1) and the gyri cinguli to the occipito-frontal bundle (OF) and thence to the central area (CA). –.–.–.– the pyramidal tract arising from the central or pre-Rolandic area (after Schuster and Casper).

This is of little or no clinical value, for if we know the state of the ventricles in a given case of increased intracranial tension, a fact best established by ventriculography, we would also be aware of the presence or absence of a tumour in the frontal lobes. Therefore, it would be of much more value to establish some other criterion upon which we could judge the value of reflex-grasping in a given case. In the two cases reported here and in Janischewsky's Case No. 6 the reflex-grasping was bilateral. As Freeman and Crosby pointed out, one cannot attach as much value as a localizing sign to bilateral reflex-grasping as can be attached to the existence of this sign on one side alone. This fact would seem to be of considerable importance in the evaluation of this sign. In thirty-five cases, including the two reported here (see Schuster and Casper and Fedorovoa), reflex-grasping was unilateral in twenty-six and bilateral in nine.

In those cases in which the phenomenon was unilateral, especially in the seventeen cases of neoplasm, the lesions are constantly located in the contra-lateral frontal lobe, with the possible exception of Fedorovoa's Case No. 6, in which the exact location of the tumour was not determined. Of those cases in which the sign was bilateral there are three, the cases reported here, Janischewsky's Case No. 6 and possibly Fedorovoa's Case No. 6, in which there was no involvement of the frontal lobes. In Fedorovoa's Case No. 5, there was reflex-grasping on the right side and a complete hemiplegia on the left. As reflex-grasping is known to disappear in the presence of a complete hemiplegia, it is possible that reflex-grasping may have been present on the left at one time. In two other instances, Cases 3 and 4 of Freeman and Crosby, the frontal lobes were involved in a generalized atrophy of the brain which was most marked in the frontal region. In Case 3 there were no focal lesions. In Case 4 there were two infarcts, one in the tissue underlying the left gyrus rectus and the other in the anterior limb of the internal capsule. In this case the white matter of the frontal lobes alone was atrophic. In the other three cases of bilateral reflex-grasping the lesions were in the frontal lobes. In Janischewsky's Case No. 2 the reflex-grasping was bilateral, more marked on the left side than the right, and autopsy revealed a large glioma involving both frontal lobes and the corpus callosum. In Freeman and Crosby's second case reflex-grasping was marked on the right side and slight on the left. Autopsy in this case revealed a tuberculoma on the medial surface of the left frontal lobe which compressed the corpus callosum and involved the right frontal lobe to a slight extent. Mayer's [7] Case No. 2 presented bilateral reflex-grasping, and at autopsy a glioma was found in the anterior part of the corpus callosum which extended into the white matter of both frontal lobes, the head of the caudate nuclei and on one side to the anterior portion of the putamen.

From these cases we may conclude that bilateral reflex-grasping may in some cases result from bilateral involvement of the frontal lobes, but in a large percentage of cases it was present in the absence of any demonstrable lesion of the frontal lobes, or was associated with generalized and vague lesions. It is thus obvious that bilateral reflex-grasping is of no certain value as a localizing sign.

It might be well to state that it is not the purpose of this article to attempt to detract from the work of previous observers which seems to establish the value of this sign, when unilateral, in the localization of frontal lobe lesions. The number of cases in which this contention has been borne out is far too great. However, as in the case of all other clinical phenomena, a given sign is only of real value when we are aware of its indications in a given case and its limitations under known conditions.

CONCLUSIONS.

(1) Two cases of tumour of the brain in regions other than the frontal lobe in which marked bilateral reflex-grasping was present, are reported.

(2) Reflex-grasping in the presence of a marked internal hydrocephalus with increased intracranial tension is of little localizing value. This is particularly true when the sign is present bilaterally.

(3) Bilateral reflex-grasping is at all times of questionable value as a localizing sign.

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THE RATE OF CONDUCTION IN THE HUMAN MOTOR NERVE.

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THE velocity of conduction of impulses in human motor nerves has, in spite of numerous investigations, remained an unknown quantity up to the present. The comparative paucity of recent work, in the face of the unsatisfactory nature of all previous results, may possibly be due to a certain lack of interest in an apparently academic problem. This attitude seems to be fundamentally wrong. As the formulation of reflex mechanisms increases in precision, the time may well arrive when temporal measurements will afford a clue to the better understanding of the particular elements involved in a nervous reaction.

The figures for the velocity of nerve impulses available at present not only show a complete lack of agreement between the various observers, but in the hands of no single observer are the results consistent. This will clearly be seen from the following table of velocities in human motor nerves.

Observer	Mean velocity per second	Maximal value	Minimal value	Nerve	Site of stimulation
Helmholtz and Baxt (1867)	39·9 m.	37·5 m.	31·0 m.	Median	Wrist and upper arm
Kohlrausch (1866)	94 m.	—	—	—	—
Donders (1868)	26 m,	—	—	—	—
Helmholtz and Baxt (1870)	64·56 m.	89·4 m.	36·47 m.	Median	Sulcus bicip. internus and wrist
Place	35·25 m.	62 m.	17·24 m.	,,	Lower margin of deltoid and wrist
Oehl	Warming 50 m. Cooling 25 m. Normal 30 m.	78 m. 35 m.	36 m. 20 m.	—	—
Alcock	66·8 m.	—	—	—	—
Hermann	41·85 m.	—	—	—	—
Piper	120 m.	131-139 m.	107-113 m.	Median	Sulcus bicip. internus axilla
Münnich	66 m.	81 m.	55 m.	,,	,, ,,
Schaffer	64·3 m.	74 m.	54·4 m.	Sciatic	Electric stimulation deep reflexes
Felix	45·50 m.	63·4 m.	43·5 m.	,,	,, ,,

Previous to the experiments of Piper, all observers had depended on some form of mechanical registration of the muscle response, and their results had given figures which, however discordant *inter se*, agreed in assigning a velocity of less than 100 m. per second to the motor nerve. Piper, for the first time, obtained electromyographic records of the voluntary contraction of human muscle by means of the string galvanometer, and was then led to estimate the velocity of conduction in the median nerve by stimulating it with break induction shocks in the axilla and in the bicipital groove, the current produced by the muscular response being led off from the muscles of the forearm to an Einthoven galvanometer. The conduction times obtained were far from uniform, ranging between 107 and 139 m. per second. The mean velocity was estimated at 120 m. Dodge claims to have confirmed this result, without, however, publishing any figures; using a very rapid falling-plate camera, one of us has obtained values between 120 and 145 m. per second with the Piper method.

Munnich, using the same points of stimulation, adjusted the relative strengths of the two stimuli in such a way that the electromyograms obtained were exactly congruent when superimposed. His measurements also showed wide variations (81 to 55 m. per second), but gave a mean velocity of about half that claimed by Piper.

Schäffer stimulated the sciatic nerve in the popliteal space and at the level of the hip-joint, and obtained a mean velocity of 64 m. This is almost identical with Münnich's figure, with practically the same limits of variation (74 to 54·4 m. per second).

Hoffman observed that the stimulation of the motor nerve to a muscle (by a single induction shock) causes, in the intact animal, a secondary reflex electrical response to follow the original direct response. Felix made use of this observation, and recorded this reflex response in the short extensors of the toes, stimulating at the internal malleolus; in the calf muscles, stimulating in the popliteal space; and in the muscles of the forearm, stimulating the median at the elbow-joint. He calculated the velocity of the impulse from the length of nerve tract involved in the reflex arc, and found a mean velocity of 45 to 50 m. per second. Although his extreme figures are 63·4 and 43·5 m., the mean deviation is relatively smaller in his results than in those of other observers.

It is obvious that this wide divergence of measurements, from the values of Piper downwards, cannot be explained by the possibility of a functional variability alone. Münnich was the first to point out two potential sources of error in Piper's method. The first lies in the assumption that an electrode, placed over a deeply-seated nerve, produces strictly local stimulation of that nerve. Such localization is only possible where the nerve is practically subcutaneous, and it was found experimentally that the area of spread of potential excitation is proportional to the amount of tissue intervening between electrode and nerve. Secondly, Piper was forced to use a far greater strength of current for the stimulation of the median nerve in the axilla, where it is deeply placed, than in the bicipital groove, where it is superficial. There was thus a second factor making for the spread of the area of excitation, quite apart from the fact that the electromyographic responses from the two points of stimulation were of different sizes.

It was by paying great attention to the latter point that Münnich claimed to have obtained results far more reliable than those of Piper. He discarded all records in which the two curves could not be accurately superimposed, so that his calculations were based on strictly comparable responses. In spite of this precaution, however, the above quoted figures of Münnich show too much divergence to be of value. That this divergence is inherent in his method and independent of the fallacy connected with the position of the nerve and the size of the muscular response is obvious from his experiments on the exposed motor nerves of animals where the proximal and distal stimuli were of the same strength. In these experiments, moreover, differences of temperature were also taken into account, but neither precaution led to a greater uniformity of results. The results are shown in the following table:—

Temperature	Animal	Length of nerve	Minimal value	Maximal value	Mean velocity per second
38·9°C.	Rabbit	61 mm.	59 m.	64 m.	61 m.
38°	Cat	73	67	82	75
38·2°	,,	80	81	82	81
38°	Dog	72·5	77	102	88
38°	,,	77	59	65	61
37·8°	,,	90	70	92	85

A reconsideration of the problem has revealed at least two other sources of error which were not excluded in the methods hitherto employed, and which may well be the cause of the lack of agreement among results in the past.

An inspection of the electromyograms published by Münnich shows that the exact point of inception of a curve cannot be determined with accuracy, but that they admit, at their best, of a possible deviation of 0·5 sigma in either direction. In some of the published records the possible error is considerably greater. When dealing with short stretches of nerve, as in the animal experiments, an error of 0·5 sigma may double the estimated velocity; but even where greater lengths of nerve tract are involved—e.g., 19·5 cm. in man—the same error can shift the estimated velocity from 66 to 55 m. on the one hand, or to 78 m. on the other. The electromyograms of Schäffer and Felix, which were taken at a slower speed than Münnich's, show an even greater possible error, while Piper's original records were photographed at a very high speed and are relatively, though not wholly, free from it.

All previous observers have used the break induction shock for stimulation, and it is in this that the second source of error lies. Bernstein showed that the duration of a break induction shock may amount to 2 to 3 sigma. Thörner, using an inductorium with an iron core, in circuit with 2 cm. of nerve, gives the duration as three sigma.

The importance of this for the experiments under consideration was emphasized by Steinhausen, who pointed out that we have no means of telling at what point, in the course of the three sigma, the nerve impulse is actually transmitted; that is to say, what phase of the wave of potential represents the effective concentration of current for stimulation. Even in experiments on isolated nerves, where the two successive shocks are delivered with the coil distance unaltered, it must not be assumed that the effective concentration of current is reached at identical points on the two curves. If now we turn to the experiments on human subjects, where the nerve has to be stimulated successively in superficial and in deep positions, so that different intensities of current have to be employed, it is fairly certain that stimulation will occur at appreciably different points on the potential curves.

Concerning the method to be described, it is claimed that the sources of fallacy detailed above have been excluded, and the following requirements satisfied :—

The point of inception of the muscle response can be established within a limit of error not exceeding 0·08 sigma; this error is, for practical purposes, negligible.

The stretch of nerve between the two stimulated points can be measured within an experimental error of ± 2 per cent., a far smaller figure than could obtain in previous experiments.

The stimulating electrodes are not separated from the nerve by any tissue other than skin and a thin layer of superficial fascia.

The duration of the stimulating current is below 0·1 sigma.

METHOD.

The essential feature of the method is the use of a pendulum or spring contact breaker, by means of which a given circuit can be closed and broken again within an exceedingly brief interval. The second important feature is the substitution of a condenser discharge for the break induction shock in stimulation.

The contact breaker (spring type of Keith Lucas) has two keys; one fixed and one movable along a graduated arc. In the present experiments the first key was used for the administration of the stimulus (condenser discharge), while the second key was connected in series with the string galvanometer, by means of which the resultant muscle twitch was registered. Both keys are worked by the release of a loaded steel spring which swings horizontally over the graduated scale at a fixed rate; the time equivalent of one division on the scale is 0·175 sigma. Each key (model used by Keith Lucas with his pendulum) consists of a steel pin held in electrical contact with an adjustable knife edge by means of a small spring In the original design the swing of the loaded springhead knocked the steel pin from the knife edge into a neutral position, thus breaking the circuit. For the present experiments the first key had to be modified in such a way that electrical contact only existed momentarily while the springhead was passing over the steel pin. This was achieved by bringing the springhead, instead of the

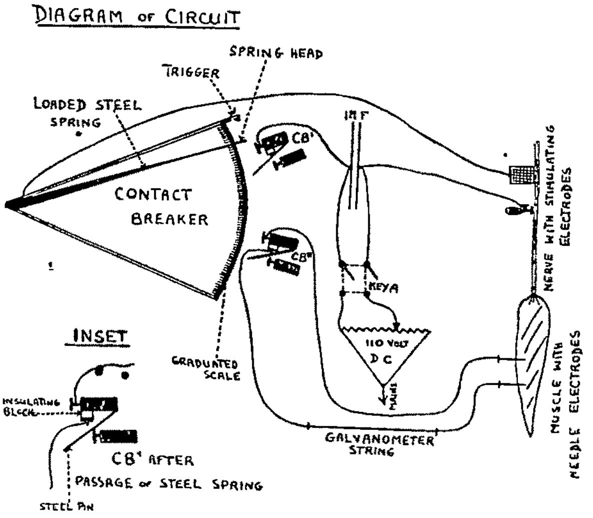

FIG. 1.—Diagram of circuit.

knife edge, into circuit with the steel pin, electrical connection depending on the fact that the free end of the steel pin, by virtue of its elasticity, yields slightly to the impact of the springhead, and its contact with the knife edge is not broken until it has been in contact with the springhead for an instant. The second key was used as a contact breaker, the swing of the springhead throwing the galvanometer out of circuit. In this case it was necessary to slip an insulating sleeve over the projecting end of the steel pin, so as to avoid cross-connection with the stimulating circuit via the springhead. The galvanometer was a double string Cambridge model, but one string only was used in these experiments.

PROCEDURE.

The Lucas keys CB′ and CB″ were set as shown. The source of current, a 1 MF condenser, was charged from the mains by momentarily closing key A. The loaded spring was then released by pulling back the trigger, and it knocked the keys CB′ and CB″ into the position shown in inset. The charging voltage could be varied by means of a rheostat, and was adjusted so that the condenser discharge produced a submaximal stimulus with an easily bearable sensory effect.

The nerve chosen for stimulation was the ulnar nerve, and the points stimulated were in the ulnar groove at the elbow-joint, and a point at the wrist where the nerve becomes superficial on displacement of the flexor carpi ulnaris tendon. In both positions the nerve is virtually subcutaneous, and the area of stimulation was restricted to a minimum by using a small button electrode which could be pressed well against the nerve. In each case the indifferent electrode consisted of a large padded zinc plate, bandaged over the upper arm. The electrodes were connected to key CB′ as shown in the diagram.

The recording electrodes were two fine steel needles, connected in series with the galvanometer and the second key (CB″); these were plunged into the substance of the abductor minimi digiti muscle, about 2 cm. apart, and placed in line with the long axis of the muscle. The proximal needle was about 4 cm. from the stimulated area at the wrist.

It will be evident from the connections of the recording circuit that the registration of a muscular response is only possible before the springhead has passed key CB″. If, therefore, CB″ be moved so close to CB′ (stimulus) that the galvanometer is thrown out of circuit before the response has occurred, there should be no galvanometer deflection other than that due to the polarization current of the skin and the capacity effect of the subject's body. It was found that the capacity effect could be easily rendered negligible by providing a permanent leak with a resistance of 10,000 ohms between the needle electrodes. The polarization effect, with the type of needle used, was of a far smaller E.M.F. than the action current. It was therefore possible to adjust the galvanometer so that the polarization current caused no deflection at a sensitivity at which the current of action was still appreciable. During an experiment the presence or absence of a galvanometer deflection was observed directly. The stimulating electrode was first placed over the nerve in the ulnar groove and key CB″ moved up opposite CB′. In this position stimulation produced of course no galvanometer deflection. CB″ was then moved away from CB′ until a deflection in response to stimulation could just be observed. The point at which the galvanometer response occurred could be localized with great sharpness to within half a division on the scale, that is, to 0·08 sigma. In every instance the genuineness of such a positive result was verified by a blank experiment, in which the experimental conditions were identical except that the button electrode was not on the ulnar nerve, but at some neutral point on the forearm. A uniformly negative result in these circumstances was accepted as proof that the galvanometer excursion actually represented the contraction of the abductor minimi digiti muscle. All positions on the scale beyond that point obviously gave positive results. Let the point be known as position A.

In the second set of experiments the whole procedure was repeated, but with the button electrode at the wrist. In this case the distance between CB′ and CB″—when a galvanometric response was first obtained—was very short. This position of CB″ was denoted point B. The time equivalent of these two points then represents the time taken by the nerve impulse to travel from the stimulated area at the elbow to that at the wrist.

To determine the time taken by the springhead to pass from position A to position B, both keys were converted into contact makers and connected each with one string of the galvanometer and a millivolt charge circuit. The strings were so adjusted that closure of the circuit deflected each string sharply and through the same distance. Simultaneous photographs of the deflections due to successive making of the keys were taken during the swing of the springhead at fairly high speed. The velocity of conduction was calculated from the data thus obtained and from the length of nerve measured between the two stimulated points.

The velocity of motor nerve conduction was studied exhaustively in the subject G. The results are tabulated below:—

ULNAR NERVE.

Date	Latent period electrode at wrist	Latent period electrode at elbow	Nerve length	Mean velocity
13.7.31	6 sigma	8 8 sigma	31 cm.	37·8 m. per sec.
15.7.31	6	8·7-8·9	31	38·2-37·3
22.7.31	6	8·8	31	37·8

Needle electrodes in abductor minimi digiti muscle, 4 cm. from stimulating electrode at wrist.

Velocity of nerve impulse = 37·8 m. per second.

On each of the dates some twenty or more observations were made, and in each case, except in some of the readings of the 15th, no perceptible variations were noted. In other words, the efficiency of the method is such that no significant discrepancies of results are encountered. Were it possible to measure the length of nerve between the two points of stimulation with equal accuracy, the velocity of conduction could be determined within 1 per cent. of error. This is unfortunately not the case, the possible error in nerve measurement being + or − 1 cm.

In the above cited results a nerve length of 32, instead of 31 cm., would raise the velocity from 37·8 to 39·2 m. per second; and a nerve length of 30 cm. would bring it down to 36·5 m. per-second.

This difficulty of accurate measurement should not be insuperable, given a sufficiently large number of observations on dissecting-room material from which the relationship between nerve length and length of ulna from olecranon to styloid process could be worked out with accuracy.

In a further attempt to settle this point a series of observations were made on the same subject using three points of stimulation of the ulnar nerve.

The distal point remained as before at the wrist; the middle point was just below the ulnar groove and 29 cm. from the wrist, while the proximal point was 2 cm. above the original site at the elbow, the electrode being pressed well on to the nerve, displacing the triceps tendon outwards; this point was exactly 35 cm. from the wrist electrode. The figure for the distal electrode still remained 6 sigma; for the middle electrode it became 8·2 sigma, and for the proximal electrode 9·5 sigma; the velocities for these two positions were 38·3 m. and 39·1 m. per second respectively. These results are in fair agreement with the original set of figures, when the fact is taken into consideration that the proximal stimulus—on account of the slightly deeper position of the nerve—is not strictly comparable with the others.

Three other subjects offered themselves for experiment and gave the following results :—

ULNAR NERVE.

Date	Subject	Latent period electrode at wrist	Latent period electrode at elbow	Nerve length	Mean velocity
23.7.31*	T	6 sigma	9 2 sigma	31 cm.	36 m. per sec.
29.7.31	H	6	8	26	35·1
30.7.31	J	6	8·2	28	36 8

Needle electrodes in abductor minimi digiti muscle, 4 cm. from stimulating electrode at the wrist.

In each of these subjects repetition of the experiment gave identical readings on some twenty occasions. We regard the lack of uniformity of the results of these three subjects *inter se* and their divergence from the values obtained on subject G as being an expression of the difficulty of assessing with accuracy the length of nerve between the points stimulated.

In only one subject (G) was the median nerve used for a similar experiment, and in this case the needle electrodes were plunged into the small muscles of the thumb on the thenar eminence. This nerve was far less suitable than the ulnar, owing to its deeper situation. Again, the most superficial parts of it were chosen for stimulation, the distal point being at the wrist, where on lateral displacement of the flexor tendons the nerve could be pressed against the styloid process of the radius ; the proximal point where the nerve lies along the medial border of the biceps, the electrode being pressed outwards and under the edge of the muscle. The distance between these two points was 39·4 cm., and the distal electrode was 5 cm. from the needle electrodes. The figures obtained were 7 sigma for the distal point, and 11·4 sigma for the proximal point, giving a velocity of 36·8 m. per second.

In three subjects additional readings were taken for stimulation of the ulnar nerve in the axilla, and in one subject for stimulation of the median in the axilla. The results are given below :—

ULNAR NERVE,

Subject	Latent period electrode at wrist	Latent period electrode at axilla	Nerve length	Mean velocity
G	6 sigma	15 6 sigma	62 cm'	41 m. per sec.
G	6	15	62	43
T	6	14·7	60	43
J	6	13·7	56	42·7

MEDIAN NERVE.

Subject	Latent period electrode at wrist	Latent period electrode at axilla	Nerve length	Mean velocity
G	7 sigma	13·6 sigma	56 cm.	43 m. per sec.

These readings were taken more for the sake of completeness than with a view to corroborating former results. They agree, *inter se*, very closely, but cannot be accepted as valid, because of the greatly exaggerated possible error in nerve measurements. The nerve not only passes over two joints so that the estimates vary according to the position of the joints, but it is deeply seated in the axilla, thus affecting both the localization of stimulus and the accuracy of measurement. The results obtained from the ulnar nerve in the forearm are therefore held to be the nearest approach to a true value for the velocity of conduction of motor impulses.

Though these experiments afford no evidence that there is any appreciable difference in conduction rate between the upper and lower portions of a motor nerve, such as the ulnar, it was thought possible that the velocity of conduction in its terminal intramuscular branches might be reduced. In a study of the human deep reflexes by one of us in conjunction with Dr. Cook it was pointed out that, with direct electrical stimulation, the rate of propagation of a contraction along the rectus femoris muscle was 20 to 30 m. per second (stimulus=single induction shock). Owing to the obvious difficulty of accurately localizing the point of stimulation in this case, we decided to repeat the experiment on the same muscle, but with indirect stimulation—using the patellar reflex response. Before selecting two points on the muscle from which the electrical response was to be led off, it was necessary to determine the level of entry of the nerve, or the "nervous equator" of the muscle. Only then could one be sure of the direction of the response. The muscle was accordingly explored along its entire extent by two pairs of needle electrodes set 2 cm. apart, and moved successively from a proximal position near its origin, to within a short distance from the upper border of the patella. In a muscle measuring 43 cm. in length, the nervous equator was found to be represented by a transverse band, 3 cm. broad, lying about 14 cm. below the anterior superior spine. Above this band, the electrical response travels upwards; below it it travels downwards. When one electrode is placed just above the band, and one just below it, the electromyogram presents a triphasic curve. Piper had already drawn attention to this triphasic response whenever the electrodes happen to be placed athwart the nervous equator. In a discussion of its significance, he offered what appears to be a convincing explanation of its origin, namely, that it represents the resultant of the ascending and descending action currents. In a criticism of the interpretation of similar triphasic curves, recorded by Golla and Cook, Pritchard casts doubt on Piper's view. Fig 2 is a reproduction of Piper's original diagram.

Fig. 3 shows the reversal of the direction of the electrical response above and below the nervous equator, and the triphasic response when the electrodes are placed athwart the narrow band of the nervous equator.

Having determined the position of the nervous equator, it became necessary to ascertain whether the contraction reached all points on any particular transverse level of the muscle simultaneously. This was done by leading off from two pairs of needle electrodes, each connected to one string of the galvanometer, and plunged into the muscle along a straight transverse line. The response was found to be simultaneous in the two pairs.

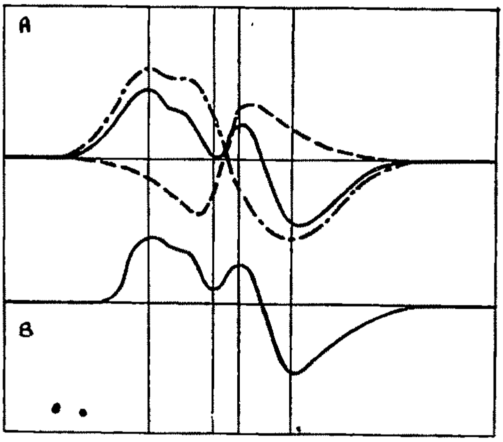

FIG. 2.—Diagram after Piper. In the group A, curve —.—.—. represents an actual electromyogram from above the nervous equator, and curve — — — an actual electromyogram from below the nervous equator. The unbroken line is the resultant of the two curves superimposed. B represents an actual electromyogram obtained from electrodes, one above, and one below the nervous equator. Note the very close correspondence between this curve and the above, arrived at by calculation.

Measurements of velocity in intramuscular nerve fibres could now be undertaken and were made in the manner just described, but with the two pairs of needle electrodes 12 cm. apart; both pairs, of course, were below the nervous equator, so that the response was unidirectional. The distance between the needles in each pair was about 0·5 cm. Fig. 4 shows the electromyogram of the patellar reflex thus recorded. The velocity of the descending response is 29 m. per second, or 10 metres slower than in the ulnar nerve. As some difficulty was experienced in obtaining good electromyographic records with strings loose enough to respond to such small currents, the experiments were repeated with the inclusion of two-valve amplifiers in the circuits, giving a tenfold amplification of the muscle currents. The strings could now be kept at a fairly high tension, and gave sharp and accurately readable deflections. Measurements of these showed a velocity of 29 m. per second—that is, identically the result quoted above.

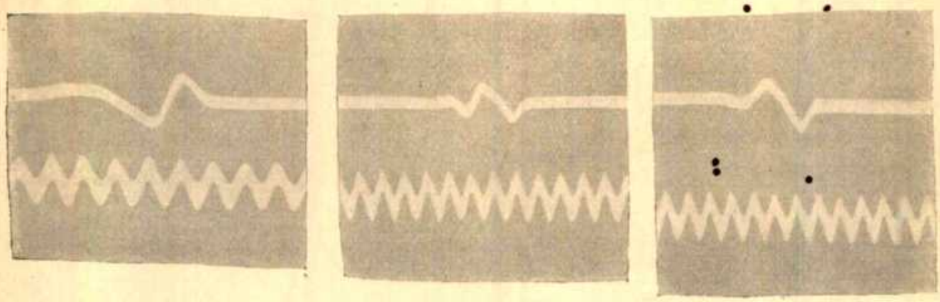

FIG. 3.—Electromyograms of rectus femoris from three positions. Left curve obtained with both electrodes above the nervous equator; middle curve with one electrode above, and one below; right curve with both electrodes below the nervous equator.

Fig. 5 represents the electromyograms obtained from needle electrodes 8 cm. apart in response to a single stimulus (induction shock, administered at the brim of the pelvis). Again, the impulse can be shown to travel at the rate of 29 m. per second.

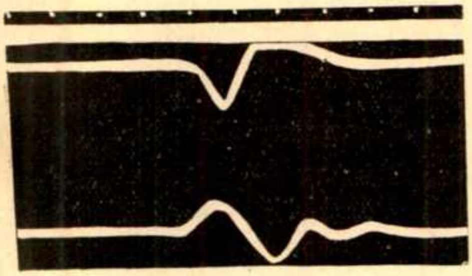

FIG. 4.

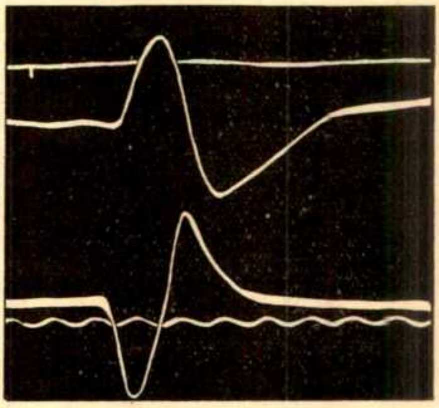

FIG. 5.

.—Electromyogram of knee-jerk led off from two points on the muscle 12 cm. apart. Top line: Time = ·01 sec. Lower record represents response from proximal point.

FIG. 5.—Electromyogram of rectus femoris, in response to break induction shock, recorded by two strings. Lower record represents the response at a point 8 cm. above that recorded by the upper curve. Time = ·01 sec. Uppermost line = stimulus.

The time interval between the responses to stimuli administered at two distant points on a nerve is an expression of the velocity of the nerve impulse, no other factor being involved; the interval between the action currents led off from two points of a muscle in response to a single stimulus does not only depend on the velocity of conduction of the impulse in the motor nerve, but also on a delay referable to the motor nerve ending. This terminal delay, which has been observed by Fulton, Fuji, Forbes, Ray and Griffith, was attributed by Fulton not to the end-plate, but to diminished conductivity in the finer intramuscular nerve filaments. There is no experimental evidence of such diminished conductivity. Samojloff's assumption of a higher temperature coefficient for the conductivity of the nerve-plate, as against that of the nerve-fibre, would appear to provide an argument against Fulton's view. The so-called end-plate delay is of the order of about one sigma in the mammalian muscle. This factor being now taken into consideration, the discrepancy between the results obtained by the two methods of approach is explained. Turning back to the ulnar nerve experiments, the velocity of conduction was found to be 39 m. per second, or 3·9 sigma elapsed between the muscle contraction in response to the proximal and the distal stimuli. In the quadriceps experiments, the nerve impulse in travelling from one point of the muscle to the other must traverse the motor end-plate. Assuming the end-plate delay to be about one sigma, correction for this brings the apparent velocity of 29 m. to an actual velocity of 39 m. This result shows, incidentally, that there is no grouping of the reflex motor discharges at the proximal and distal points of the muscle. The muscle then does not contract as a whole in the reflex response, although we have reason to believe from the work of Isayama and Fulton that the response is compounded of successive volleys.

The Velocity of Conduction of Afferent Impulses.

A number of experiments were designed and carried out with a view to ascertaining the velocity of conduction on the afferent side. The observation of Hoffmann's, that a single induction shock applied to a motor nerve produces—in the intact human being—a secondary reflex electrical response following on the original direct response, had already led Schäffer to attempt an estimation of the velocity of sensory conduction by stimulating a motor nerve at two points as distant as possible, and noting the time relationship of the reflex responses. The method would appear to be a valid one, since Schäffer clearly showed that the reflex response was not due to a proprioceptive stimulus resulting from the primary contraction, but to actual stimulation of afferent fibres in the motor nerve itself. The results of Schäffer show, however, such wide variations, that they are valueless. This is to be attributed, *inter alia*, to the impossibility of determining the exact point of stimulation of a deep-seated nerve, such as the sciatic. It seemed possible that stimulation of the ulnar nerve at its two superficial points, and searching for the reflex contraction in each case with the aid of the spring contact breaker, might offer a means of arriving at the velocity in sensory nerve conduction. Numerous experiments, however, failed to detect a secondary reflex response from the abductor minimi digiti muscle, whether the stimulus were a condenser discharge or a break induction shock. One can only conclude that the Hoffmann reflex does not occur in this muscle, but is possibly confined to muscles which are more closely associated with postural function than the small muscles of the hand. The method would appear to be inapplicable in the intact human being, since, unfortunately, nerves supplying postural muscles are mostly deeply seated, and offer at most a single point of access where localized stimulation is possible.

RATE OF CONDUCTION AND REFLEX TIMES.

The accurate determination of the rate of conduction of motor impulses is only one step in the analysis of the time relations which figure in a reflex response. Velocity of conduction on the afferent side is the second step. There is no warrant for the assumption that afferent conduction takes place at the same rate as efferent. What little is known about the rates of certain types of afferent impulses makes this assumption exceedingly unlikely. Erlanger and Gasser have shown that in the mammal sensory fibres can be divided into two groups: one with a velocity of conduction varying between 30 and 80 m. per second, and one with a velocity of 0·7 to 1·3 per second. Adrian observed that a light touch on the ulnar side of a cat's paw gave rise to impulses of high action potential, probably conducted at a rate of 50 m. per second, or more, and others of less potential, the records of which suggest that they may travel as slowly as 15 to 20 m. per second.

There is some reason for associating fibres conducting impulses of high potential with sensibility to light touch, and those of lower potential with a class of receptor that would give rise to pain on intense stimulation. In the cat, Dennig found a rate of 40 m. for the sensory fibres in the splanchnic, and Eccles and Sherrington a rate of 30 m. for the afferent impulses concerned in the flexor reflex of the leg. Discarding the results of Schäffer, which one is inclined to do on account of their inconsistencies, no information remains as to the rate of conduction of proprioceptive impulses from tendon joints and muscles. It is certain that until values for afferent conduction are available, comparable in accuracy with at least the present series of motor values, no attempt can be made to calculate the central delay in reflex action. Even when the requisite values for velocity are at hand, a further factor remains for which allowance will have to be made, namely, the continued discharge of a receptor in response to however brief a stimulus. It can only be predicted that, if our values for the rate of motor conduction be accepted, a very much higher rate will have to be assigned to proprioceptive afferent impulses in order to account for the commonly observed values of the latent period of tendon reflexes. Hoffmann, adopting Münnich's figure of 66 m. per second for both afferent and motor conduction, calculated the central delay for the deep reflexes in man, and occasionally obtained negative values. This obvious impossibility would have obtained still more frequently had he made due allowance for the time lost at the receptor organs.

SUMMARY.

A new method is described for the estimation of the velocity of motor nerve impulses in the human subject.

The conduction rate of the ulnar nerve is found to be 38·7 m. per second with a possible error of not more than 5 per cent. The relation of these results to previous estimates and their bearing on the time values of the deep reflexes is discussed.

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NOTE ON THE ACTION OF CURARE IN TETANY.

BY H. HARTRIDGE AND RANYARD WEST.

(From the Physiological Laboratory, St. Bartholomew's Hospital.)

IN a recent contribution to this journal [1], the selective removal of the tonic, clonic and fibrillary muscular contractions of parathyroid tetany in the dog was recorded. This was effected by a fresh watery extract of a curare supplied by Messrs. Burroughs Wellcome and Co., who obtained it from an unknown source.

Repetition of this work, with new samples of curare, yielded the following results. Of seven samples tested, two only show the selective action under consideration. In the active samples the selective agent stood boiling and autoclaving, at least in some degree. A watery extract deteriorated, so that the selective action vanished in a few months, leaving the paralytic action, which was, however, somewhat impaired.

It has not been possible to relate the variation in this property of the various curares to their sources in every case, but "Calabash" and "Pot" curares occurred in both groups.

A paper is in course of preparation by one of us [2] showing a similar and parallel variation in the action of curare upon certain rigid conditions in man.

It is not the purpose of this note to consider the theoretical implications of these findings. Bremer, as a result of a very full study [3], [4], [5], [6], [7], of the selective action of curare in decerebrate rigidity and local tetanus, concludes that these are manifestations of Wedenski inhibition, so that "the tonic impulses continuously arriving at the neuromuscular junction of the fibres engaged in postural tone are blocked" at a time when "the junctions of the resting, unfatigued fibres are able to transmit single motor-volleys or brief tetanic reflex discharges."

Other theoretical possibilities are dealt with in our previous paper. But at this stage we think it should be suggested that a second active principle may be present either in the principal plant ingredient (usually *Strychnos toxifera*) or in some of the various other ingredients which contribute to the "curare" which reaches the market. We feel that the time is ripe for a full chemical assay of curare, and this is being undertaken.

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[5] Bremer and Titeca. *Ibid.*, 1928, **99**, 624.
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NOTICES OF RECENT PUBLICATIONS.

Les Tumeurs des Centres nerveux et des Nerfs périphériques. (Atlas du Cancer, 9 and 10 fasc.) Par G. ROUSSY et CH. OBERLING. 12 plates with descriptions. Paris: Félix Alcan. 1931. Price 80 francs.

Under the ægis of the French Association for the Study of Cancer, the authors have given us a monograph on the pathology of the gliomas and neurofibromas richly illustrated with drawings. Although the arrangement is that of an atlas, the twelve large and closely-printed pages of text contain a more detailed histological description of the various types of glioma than is to be found in any textbook. As those who know their work would expect, the authors form their own classification, which differs from that of Bailey and Cushing in several ways. And while certain of the names chosen by these authors, such as "ependymoblastoma" and "glioblastoma" are used, others such as "astroblastoma," "spongioblastoma" "medulloblastoma" and "medullo-epithelioma" are discarded. The authors do not recognize the distinction of the first of these forms from the astrocytomas, considering that the cells which resemble astroblasts are the result rather of the de-differentiation of adult astrocytes than of the perpetuation of the astroblast stage. For this opinion there is considerable justification. But the reason given for classing polar spongioblastomas with the oligodendrogliomas is less clear. As is well known, polar spongioblastomas have been called by Josephy "neurinomes centrales," owing to their resemblance to neurofibromas, and the analogy of the functional resemblance of the sheath of Schwann cells to the oligodendroglia suggests to the authors that central neurinomas might be called "oligodendrocytomes fasciculés." The type of tumour for which the name medulloblastoma is now in general use they call "neurospongioma." There is good reason given for this change in the criticism that the term "medulloblast" is rather a theoretical conception than a recognized cell of the developing neural tube. In any case "medulloblasts" are supposed to appear at a later stage of development than spongioblasts. According to the assumption of Bailey and Cushing, that tumours vary in malignancy according to the stage of development represented by their type cell, medulloblastomas should be less malignant than polar spongioblastomas. But the former are the most malignant and the latter among the least malignant of cerebral tumours. The name "neurospongioma" which the present authors have adopted is less controversial, as it relates to a very early stage of development in which neuroblasts and spongioblasts are not yet fully differentiated. In some tumours of this type which they have examined the authors have found that the matrix is composed of neurofibrils, and they consider tumours of this type to be related to neuroblastomas rather than to tumours of the neuroglia. Thus included in this alteration of nomenclature there is an altered conception of the nature of the cells forming the tumours. Under the term "neuro-epithelioma" the authors include the primitive medullo-epitheliomas and the rather more differentiated neuro-epitheliomas of the retina. This seems to be an improvement, as all such tumours are rare and gradations between the more primitive and the more differentiated are not uncommon.

Ependymal tumours are classed in three groups, ependymocytomas, ependymoblastomas and ependymogliomas. A clear description is given of these tumours and the various types are well illustrated by the plates.

Perhaps more important than this re-classification is the conception that gliomas do not necessarily grow from cell rests, but may equally well arise as the result of de-differentiation of adult cells. For certain forms, such as the neurospongiomas and neuro-epitheliomas, the authors accept an embryonic origin, but for the others they incline towards the widely accepted view of anaplasia.

In their short chapter on neurofibromas the authors keep to the traditional view of the French school that neurofibromas arise from the sheath of Schwann. They distinguish these growths from plexiform or "true" neuromas, although they accept a similar origin for the latter.

The coloured plates are excellently drawn from sections stained by hæmatoxylin and anilin dyes. The appearances obtained by metallic impregnations are also given in a few line drawings of individual cells. As the authors claim in their preface, it is valuable to be able to say that a microscopic section corresponds to an illustration, whatever may be the name or theory of origin given to the tumour at a later date. It is therefore a little disappointing that many well-known types of tumour, especially of the neuroglial and ependymal groups, are not illustrated. Rather more space is perhaps devoted to the neurospongiomas than is warranted by their variations. There is, however, no limit to the number of possible illustrations in an atlas of the gliomas, and we are very grateful to the authors for succeeding so well in the difficult task to which they set their hands.

Ueber Apraxie: Eine klinische Studie. Von OTTO SITTIG. Berlin: S. Karger. S. 248. Price 24 M.

For the last thirty years Liepmann's definition and description of apraxia have been generally accepted, though considerable modifications have been suggested in his interpretation of its nature. Some authors have emphasized, even more than Liepmann did, the importance of psychological factors in its pathology; others, as the author of this interesting monograph, have insisted that it should be treated only as a physiological problem and studied by clinical methods rather than by the aid of psychological hypotheses. Sittig calls his volume a "clinical study."

It is a valuable contribution to a subject that needs re-investigation from this point of view. His own observations are recorded in detail, but so clearly and logically that even the long case histories are never tiresome. His arguments are direct and his assumptions rarely go further than his premises warrant. The literature is reviewed critically and used liberally in support of his own observations, in fact the extensive bibliography and the free quotations from other authors will make the book extremely useful to everyone interested in the subject.

Sittig, who has translated some of his papers into German, is familiar with Hughlings Jackson's methods and views and has followed him closely in his treatment of the problems presented by a study of apraxia. He regards apraxia as a disturbance of the more automatic activities, and believes that the lesions to which it is related involve the motor system at a higher functional level than those which produce hemiplegia, etc. In his most interesting case there was a severe apraxia of the trunk, while in others different portions of the body were affected; from these and other observations he concludes that apraxia follows Jackson's law that the most highly organized and complicated activities are first and most severely affected by disease.

Methoden zur Erforschung der Funktionen des Kleinhirns. Von J. TEN CATE. S. 96. Berlin: Urban und Schwarzenberg. 1931. Price 5.50 M.

This monograph forms a part of the volume on "Funktionen des Nervensystems" of Abderhalden's "Handbuch der biologischen Arbeitsmethoden," which is in course of publication. It describes in careful detail the methods of experimentation on the cerebellum which have been, or may be, usefully employed in laboratory animals, and deals more shortly with the observation of the disturbances of function and other phenomena which result from ablation, or mechanical, chemical, and electrical stimulation of the cerebellum. A short description of the mammalian cerebellum and of its chief morphological features in reptiles, birds, and fishes forms a useful introduction to the sections concerned with experimental methods.

Spezielle Chirurgie der Gehirnkrankheiten. Bd. I., Die epileptischen Erkrankungen. Heft 1. Von F. KRAUSE und H. SCHUM. Stuttgart: Ferdinand Enke. 1931. S. 520. Price Rm. 78.

The present is the first of two volumes dealing with its subject from the point of view of the surgeon. It contains a comprehensive, but non-critical, statement of modern knowledge of the incidence, ætiology, symptomatology, physiology and pathology of epileptiform convulsions and of epilepsy proper. A second volume, yet in the press, will deal with diagnosis, medical and surgical treatment and with the social aspects of epilepsy. An extensive and predominantly German bibliography is found at the end of each section.

As a work of reference this volume should prove of value to students of neurology.

Encephalitis Lethargica: its Sequelæ and Treatment. By Constantin von Economo. Translated and adapted by K. O. Newman. Oxford University Press (Humphrey Milford), 1931. Pp. 200, with 21 illustrations. Price 18s.

The German edition of this book was published in 1929 and has been reviewed in these pages. The author has added to this English edition a short section on "Conditions of the Nature of Psychoses"; otherwise the original text is unaltered. The translator has been successful in his difficult task of sailing "between the Scylla of literal translation and the Charybdis of free translation," and the result is both intelligible and readable.

It is evidence of the acuteness of the late Professor von Economo's intellect that so little has had to be changed in our conception of encephalitis lethargica since the publication of his first monograph on the disease in 1918. The descriptton of the sequelæ and of their morbid anatomy had of course to be added, but we know little more either about the ætiology or the morbid anatomy than he told us then. In particular, his conception of the disease as one in which the nerve cells were primarily affected and the inflammatory reactions by the blood-cells were merely secondary concomitants, agrees with the more modern views of virus diseases of the central nervous system. The description of the morbid anatomy in the present volume is indeed by far the most accurate and complete that has appeared in the English tongue. In this section, too, the translator's knowledge of neuropathology has been valuable, as without such knowledge translations of technicalities are apt to be incomprehensible, an error which was not altogether avoided in the English translation of the same author's book on the cerebral cortex.

Die Schadigungen des Nervensystems durch technische Elektrizität. Von F. Panse. S. 155. Berlin: S. Karger. 1930.

Electrical accidents involving the nervous system are now sufficiently common to justify the appearance of this monograph. The author has collected and analysed critically most of the information on the subject available in medical literature, and has added interesting observations of his own.

Symptoms referable to disease of the spinal cord are the most common and interesting, especially the muscular atrophies in regions corresponding to the spinal segments through which the current passed. These are attributed to vasomotor disturbances in the grey matter of the cord due directly to the current, though the fact that weeks or months may intervene between the accident and the onset of the atrophy and palsy often makes this hypothesis difficult to maintain without the assumption of secondary glial changes. Unlike amyotrophic lateral sclerosis, which some of these cases resemble, none progress to a fatal termination. In other cases the spinal symptoms are those of a spastic paresis or of a spastic ataxia, resembling the clinical picture of disseminated sclerosis. Lesions of the peripheral nerves are not common, though often assumed to be the cause of local palsies and muscular atrophy.

The remarkable resistance of a skull to the passage of a current is probably the explanation of the rarity of cerebral lesions, even when the current has passed through the head; abscesses under a necrosing area of skull are the most common complication, but occasionally signs of local or general cerebral injury are seen. The manner and the immediate cause of death after exposure to electrical currents is also discussed. In view of our uncertainty of the action of electrical currents on the nervous system, this volume is of considerable clinical and pathological interest, and the comprehensive survey of the literature that it contains makes it valuable for reference.

Manuale di Antropologia e Psicologia criminale. Applicata alla Pedagogia emendativa, alla Polizia ed al Diritto penale e penitenziario. Di B. DI TULLIO. Roma: Anonima Romana Editoriale. 1931. Pp. 367. Price L. 35.

The criminal is still the subject of active psychological and anthropological study in the country of Lombroso, and the present work gives a clear account of the conclusions reached there and the general lines of investigation. Dr. di Tullio, who is a lecturer on Criminal Anthropology in the University of Rome, won the Lombroso prize in 1929 with his work "The Delinquent Constitution," of which this is an amplified version. Following a prefatory note by Professor Ottolenghi, the author discusses the place of criminal anthropology in science and social life, its development and present status. The ætiology of crime, the physical and mental characteristics of the criminal from various points of view, biological aspects of crime, classification, prophylaxis and treatment are dealt with enthusiastically and rather discursively, but with a just recognition of the incompleteness of the work so far accomplished. The discussion of the methods of preventing crime, and the author's proposals for limiting it, are of particular interest. There is an alphabetical index of authors quoted, but not of subjects.

Zentralistiche Organisation und Seelenleben. Von JOSEF SCHEIN. München: Ernst Reinhardt. 1931. 2 Bände. S. 448 + 640. Price: Bd. 1, M. 12; Bd. 2, M. 16.

This is an essay in philosophical psychology. The first volume, on postulates, insists on the centralization or unification of psychic life. Among the general problems of habituation and subject-development, impulsive and volitional activity are contrasted, and the importance in mental development of a dominant central organ is emphasized. The second volume deals with the relation of these postulates to psychic processes and consciousness; the problem of perception is studied comprehensively. The book is one for the specialist interested in fundamentals; the author's purpose is to furnish a basis on which psychic happenings, regarded as vital processes and products of development, can be made accessible to objective investigation.

Phantastica. Narcotic and Stimulating Drugs. By LOUIS LEWIN. Translated from the Second German Edition by P. H. A. WIRTH. London: Kegan Paul, Trench, Trübner and Co., Ltd. 1931. Pp. 335. Price 15s.

Lewin's pharmacological investigations have provided the incentive for much important research in psychopathology, and an English translation of his best known book is to be welcomed. Most readers will turn at once to the chapter on Anhalonium Lewinii, where the history, uses and properties of the drug mescalin are set forth; there is interest of a similar kind in the section on Banisteria Caapi and other solanaceæ. The book offers constant evidence of Lewin's wide learning, as well as of his historical and literary interests; it is very readable.

Handbuch der Geisteskrankheiten. Herausgegeben von OSWALD BUMKE. Allg. Teil. 4ter Teil. Berlin: Julius Springer. 1929. S. 421. Price Rm. 44.

This volume concludes the general part of Bumke's system of psychiatry; it deals with therapeutics and jurisprudence.

Professor Vorkastner has written a detailed and well-arranged exposition on forensic psychiatry, which is however concerned only with German, Austrian and Swiss law. It is therefore of little practical use for English readers, but furnishes material for exact comparison with our own legal system in this connection, and is illuminating where it deals with the general problems that occur commonly in occidental countries whenever the psychiatrist is called on for expert testimony.

Dr. Nitsche's section on General Therapy and Prophylaxis is mainly devoted to definite psychotic states, the treatment of the minor forms being taken up by J. H. Schultze in another volume. Dr. Nitsche considers first psychic treatment in the wide sense, and lends little support to those who would restrict the name of psychotherapy to some special procedures of limited application. He discusses occupational therapy, medicinal and dietetic measures, hydrotherapy, seclusion, bed treatment and other problems of institutional care; the medical indications for inducing abortion and for sterilization are examined temperately, as is also the question of the propriety in individual cases of home, rather than institutional, care, with social safeguards and guidance. In a lengthy final chapter prophylaxis is considered. The whole section shows a humane and informed attitude towards matters too often clouded over by prejudice or lukewarmness. The practical details given are precise and helpful.

Professor Birnbaum has written a reflective essay on the branches of knowledge that trench upon psychiatry—cultural and social sciences of various kinds, to which psychopathology is ancillary or receptive. It is a pendant to his systematic study of the historical developments of psychiatry, in volume I.

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EDITOR.